LECTURES ON

THE LIVER AND ITS DISEASES

COMPRISING THE LOWELL LECTURES DELIVERED AT BOSTON, MASSACHUSETTS, IN MARCH 1947

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Ignem benignissima ipse anima accendit.

lectureship.

The present time seems particularly opportune for reviewing our knowledge of liver diseases. The increased frequency of infective hepatitis and its complications, during the last few years, has provided unusual opportunities for clinical observation, and its prevalence in armies, by raising it to the status of a major military consideration, has compelled its intensive investigation. Almost simultaneously the experimental approach to liver disease has expanded into a new field, and it is now firmly established that serious lesions of the liver may arise, not only from the presence of noxious substances, but from deficiency of essential nutriments. The stage is set for a great advance. The immediate tasks are to assimilate the new with our old knowledge and to effect the necessary reorientation in our views required to realize its possibilities. An attempt on this task has been made in this monograph. But it has been made in the full realization that we are too close to the new knowledge to have grasped its full implications, and any suggestions made must remain tentative and subject to revision, until sufficient time has elapsed for them to be tested more completely. At this present time it can only be hoped to define some of the questions which arise and to clear the ground of some conceptions, still in current use, which are now patently obsolete If this monograph contributes towards the solution of these necessary preliminaries it will have served its purpose.

I have to thank Dr. Balduin Lucké and the editors of the American *Journal of Pathology* for permission to reproduce Figures 42 and 43, the editors of *Clinical Science*, the *Journal of Pathology and Bacteriology* and the *Biochemical Journal* for allowing me to reproduce various figures for which acknowledgement is made in the text. I am indebted to Dr. H. C Trowell, of Uganda, and Dr. Joseph Gillman, of Johannesburg, for material from tropical cases of liver disease. Professor G. R. Cameron and Dr. M. L. Rosenheim have read the text and given me

the benefit of their valuable advice and criticism; and I am very grateful to them. Of Dr. L. E. Glynn I can only say that we have worked together for six years on the experimental and pathological aspects of liver disease and that, although he cannot be held responsible for all the views expressed here, our ideas are so interwoven that it would be impossible now to separate them with any certainty.

H. P. HIMSWORTH.

LONDON,
June, 1947.

PREFACE TO THE SECOND EDITION

THE field of research in diseases of the liver is now being rapidly opened up and, in the two years since this book was first published, several noteworthy additions to knowledge have already been made. Of these the most important is that concerning the influence of tocopherol on experimental, dietetic, massive necrosis of the liver. Not only does this finding seem to remove the discrepancies between the results from different laboratories, but it has produced facts which promise to throw light on the fundamental biochemical reactions involved in the production of hepatic necrosis, and which may not be without significance to our understanding of the human disease as it affects malnourished races. In the pathological field the surprising observation has been adequately confirmed that the condition, long accepted as 'portal cirrhosis', is, in many cases, not primarily a lesion of the portal tracts but of the central veins—an observation which makes its development considerably easier to understand. In the clinical field the syndrome of subacute hepatitis has been clarified by further experience, and light thrown on its essential pathology by the use of puncture biopsy in its early stages. On the therapeutic side our views on the uses of dietetic therapy in the different types of hepatic disease are beginning to clear. For these reasons, to record the numerous new data which are falling into their places, and to correct certain ambiguities in the original text it has become necessary to bring the original lectures up to date in a second edition.

H P. HIMSWORTH.

LONDON,

December, 1949

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LECTURES ON
THE LIVER AND ITS DISEASES

CHAPTER I

THE TYPES OF LIVER INJURY AND THEIR STRUCTURAL CONSEQUENCES

A CONSIDERATION of the immediate effects of injury upon composite organs reveals that, in general, those cells which are most highly differentiated, and which endow the organ with its characteristic function, are also those which are most susceptible to damage. Nowhere is this more evident than in the liver. In this complex organ there are, in addition to the usual vascular and supporting structures, no less than three other differentiated tissues each with its particular functions. Chief of these, and entirely characteristic of the liver, is the parenchymal cell. Less characteristic, but still highly differentiated, are the cells of the biliary tracts. Least differentiated are the Kupfer cells, representatives of the widely distributed reticulo-endothelial system. Of these tissues the parenchymal cells invariably show the severest, often the only, evidence of acute damage. Whether the injury is effected by restriction of blood supply, the introduction of poisons into the circulation, or dietary deficiency, its brunt falls on the hepatic parenchyma, and it is not unusual in recent and severe lesions to see every parenchymal cell dead while the bile ducts, Kupfer cells and supporting tissues survive apparently unscathed (Fig. 2).

Thus, in the acute hepatic lesions, parenchymal damage is the most conspicuous feature. But it is not so in the chronic. In them the most [illegible]

[illegible]

distant days of John Brown[4] and Matthew Baillie.[3,4] Originally attention centred on the hyperplastic nodules of parenchymal tissue with which such livers are studded and which Laennec,[22] to whom we



in attempting to do this we immediately come face to face with a particular difficulty.

The end results of many hepatic lesions resemble each other very closely. Just as many different acute lesions of the kidney terminate alike in a contracted fibrotic organ so many acute lesions of the liver terminate as hepatic cirrhosis. Many will remember the time when our knowledge of renal disease seemed to have reached an impasse and how that deadlock was broken by discarding the conception of renal fibrosis as an entity, and differentiating its types in relation to the appropriate antecedent lesion At this present time our knowledge of chronic hepatic disease is at a similar stage of development Just as thirty years ago 'cirrhosis of the kidney', or 'chronic interstitial nephritis' was widely considered a unity, rather than a common result of many types of renal damage, so to-day, 'cirrhosis of the liver' is still generally regarded as an entity. There are reasons for thinking that the retention of that view is one of the main obstacles to a better understanding of liver disease and, if this be so, no better contribution could be made to progress in this field than to relinquish, both in clinical medicine and pathology, the use of the term 'cirrhosis' which, not only misleads by implying an entity whose existence is doubtful, but has become so worn and defaced by loose usage as to have lost all precision. It is not proposed at this stage, however, to attempt a detailed justification of this departure from tradition. That should emerge from the subsequent discussion. All that is intended is to intimate that, when considering the types of liver injury and their sequelae, this term will not be applied to any kind of hepatic fibrosis, save in reference to the work of previous writers when the use of a new term to describe their opinions might lead to confusion.

Necrosis of the Liver

The term necrosis of the liver refers almost invariably to necrosis of the parenchymal cells Only under the most exceptional and artificial circumstances do the other hepatic tissues die Under all usual circumstances, experimental or clinical, the hepatic parenchyma alone suffers. Such a lesion can be produced in many different ways, but the necrosis always assumes one or other of two anatomical forms. In one, zonal necrosis, the damage is limited to a particular region within the liver lobule and according to its distribution is distinguished as centrilobular, periportal or midzonal (Fig 1) In the other, massive necrosis, the acute yellow atrophy of older writers, the whole lobule is involved, every parenchymal cell being dead (Fig 2), save perhaps

owe the term cirrhosis, regarded as being of the nature of new growths. Later Carswell[14] *formed a more correct conception of the condition* and, as a result of the importance he attached to the fibrous changes, the condition came to be regarded as an inflammatory and sclerosing hyperplasia of the supporting connective tissues[14 15 22] It was only at the end of the last century that importance began to be attached to parenchymal degeneration.[26] At first thus degeneration was merely regarded as the result of contraction of the proliferating fibrous tissue,[15 22] but later opinion steadily veered through the stages of regarding the two processes as concomitant,[1 21 29 30 40] to the view that the primary lesion affected the liver cells and the fibrosis and parenchymal regeneration were reparatory processes[1 20 29 30 31 37 38]

This development of ideas[35] is of more than academic interest, for ideas, however abstract, are never without their influence on practice. When it was believed that the primary process in chronic liver disease

ever, the proliferation of fibrous tissue is regarded as secondary to a

entertained It is, therefore, of the greatest importance for clinicians to be clear as to the precise implications of the different pathological lesions in the liver as, according to the significance attached to each, so will clinical research and practice be influenced At first sight it may

the dramatic advances in other fields have been the result of direct observations on patients or the development of tests of organic func-

for regeneration. As a result of these two attributes, lesions of its substance remain clinically latent until, the reserve being exhausted, illness suddenly appears. By that time the chance of arrest, let alone prevention, has largely vanished and the clinician is more often than not condemned to stand helplessly by, or at best, simply to palliate the relentless progress. This state of affairs will continue to exist until we clearly recognize the antecedent states of terminal liver damage; but

towards the edges of the areas affected where isolated, and irregularly distributed, clumps may survive. The justification for distinguishing between these two forms lies in the different course pursued by each.

Zonal necrosis is the form produced by liver poisons under ordinary experimental conditions. Its common occurrence in human disease, however, remained unsuspected until recently.[3, 16, 17, 48] After single attacks recovery occurs with astonishing speed and completeness. If an animal is given a subcutaneous injection of carbon tetrachloride, then, a zonal necrosis, centrilobular in distribution, occurs in every lobule throughout the liver[7] and, if the dose is large, this necrosis may be of such extent that only a thin cuff of parenchymal cells survive around each portal tract. Yet within a fortnight the necrotic cells have been removed, the surviving parenchymal cells have regenerated and no trace of liver damage remains.[8] This is in marked contrast to the sequence of events following massive hepatic necrosis. This lesion differs from zonal necrosis not only in its distribution within the lobule but also in its distribution through the liver. While zonal necrosis affects every lobule to approximately the same extent, massive necrosis, when insufficient to cause speedy death, is limited to particular areas which are separated by large tracts of apparently normal liver.† Areas once affected by massive necrosis never return to normal. Fibrous tissue develops at the affected sites and the final result is a distorted organ in which irregularly distributed scars cut up essentially normal liver tissue.

The broad reasons for the different results of these two anatomical forms of necrosis are not far to seek. Although in a severe zonal necrosis, far more parenchymal tissue may be killed than in many massive necroses, yet in zonal necrosis a rim of parenchymal cells survives in each lobule. This serves a double purpose. It provides a source from which new parenchymal cells can regenerate, it holds open the reticulin framework of the lobule, the Gitterfasern, as an accurate scaffolding upon which the lobule can be rebuilt (Fig. 3). In massive necrosis no such rim of parenchyma survives. In those lobules where all the cells are dead there is nothing either to prevent collapse of the reticulum (Fig. 4) or from which new parenchyma can

† It cannot be too strongly insisted upon that the terms zonal and massive apply only to the state of affairs *within* the individual liver lobule and carry no implication as to the extent of the lesion in the liver as a whole. This point is of particular importance in respect of massive necrosis. In its most commonly recognized form, the 'acute yellow atrophy' of Rokitansky large areas of liver are affected, but in the more frequent, but less well recognized lesion of so-called subacute hepatitis only a few lobules are affected in each attack. Nevertheless, whether the lesion is widespread or localized, the lesions in the lobules affected are exactly the same and lead to the same sequelae.

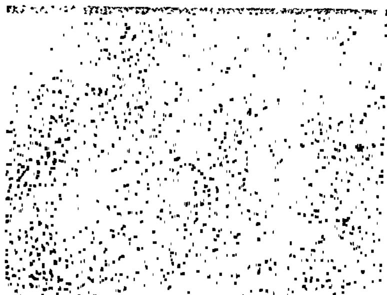


FIG 1—Centrilobular Zonal Hepatic Necrosis Rat. Subcutaneous injection of carbon tetrachloride 0 05 c c/100 g Necrosis is limited to the centrilobular zone H and E × 72

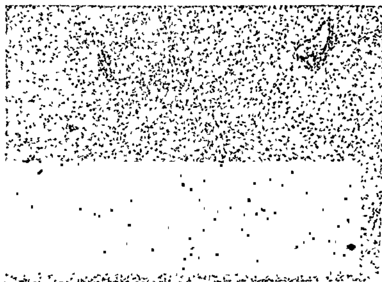


FIG 2—Massive Hepatic Necrosis. Rat. Low protein diet. All the parenchymal cells throughout the liver are dead The blood vessels and bile ducts survive H. and E. × 72.

be regenerated. In those where isolated clumps of cells survive, partial collapse of the reticulin scaffolding occurs, so that the only course open to the surviving liver cells is concentric hyperplasia with the formation of nodules of parenchymal tissue devoid of lobular pattern (Fig. 27).

The anatomical form of the necrosis thus determining the course of events, it is desirable to know if the form of injury can be related to its cause. It is speedily apparent that no accurate correlation exists. Thus a simple zonal necrosis is commonly found in infective hepatitis,[3,14,17,48] in heart failure, and after exposure to numerous poisons of which the chlorinated hydrocarbons are typical examples.[6,9,33,41,44] But, on occasions, these may lead to a massive necrosis.[19] Similarly interruption of the arterial blood supply,[11] poisoning with substances such as trinitrotoluene,[40,51] and diets deficient in protein,[54,27] may all give rise to the same massive type of necrosis. But ischaemia can also give rise to a zonal lesion. A broad, but not invariable, tendency can be seen for one type of necrosis to occur under certain conditions; but identical lesions occur from widely dissimilar causes and dissimilar lesions can occur from what is apparently the same cause.

The very different sequelae of zonal and massive necrosis do not mean that these two forms of hepatic injury are each the expression of a different pathological mechanism. In certain instances, at least, the difference is simply one of degree. Thus, when carbon tetrachloride is inhaled, ingested, or injected subcutaneously, the extent of the resulting *centrilobular* necrosis is, within limits, related to the dosage. When higher intrahepatic concentrations are reached by injecting the poison directly into the portal vein, a massive type of necrosis with subsequent scarring results.[14] Different hepatic poisons vary in virulence. Carbon tetrachloride is one of the weaker and, by natural routes, produces only a zonal necrosis. The toxin of Amanita Phalloides, on the other hand, is so powerful that in most lobules every parenchymal cell is killed, and it is only after careful search, and finding portal tracts surrounded by cuffs of parenchymal cells, that the nature of the lesion is revealed as an extreme degree of centrilobular necrosis.[14,52] Survivors of single attacks of carbon tetrachloride poisoning recover completely, survivors of poisoning by Amanita Phalloides may develop a fibrosis of the liver.[39] In these cases massive necrosis is clearly the result of the stronger action of a cause which, when acting weakly, produces only zonal necrosis. Nevertheless, despite this, the sequelae are quite different according as to whether the lesion remains zonal or progresses to the massive type.

The general conclusion from these considerations is clear: the con-



Fig 3—Centrilobular zonal necrosis Reticulin stain showing preservation of normal reticulin framework of the lobule Note the distance which normally separates the portal tract (upper left) from the hepatic vein (lower right) Rat Subcutaneous injection of carbon tetrachloride 0 1 c c /100 g Laidlaw's reticulin stain × 155

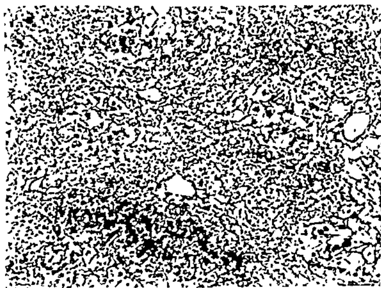


Fig. 4 [illegible]

supply is intact.[19] Parenchymal regeneration is thus dependent upon the maintenance of an adequate blood-flow to the liver. But there are also factors which interfere with regeneration even when the blood supply is adequate. It is well known that conspicuous regeneration is not a feature of the hepatic fibroses consequent upon biliary obstruction. Cameron [4] showed that transplants of liver from organs in which the bile ducts had been ligated, unlike transplants from normal livers, failed to grow. [4] Biliary retention appears, therefore, to impair the intrinsic ability of the cell to proliferate.

These considerations are clearly relevant to the problems of parenchymal regeneration in fibrotic livers. In such organs the blood supply is often grossly disarranged and the clumps of bile pigment, in the nodules of cells circumscribed by fibrosis, indicate that the outflow of bile is obstructed from those parts of the liver. But the general rule remains clear. Given an adequate blood supply and a free secretion of bile, reduction in the amount of hepatic tissue evokes proliferation of the remaining parenchyma.

Fibrosis after Injury

Fibrosis of the liver may develop after massive necrosis, after repeated attacks of zonal necrosis, following heavy prolonged fatty infiltration of the parenchyma, or as a sequel to biliary obstruction. In all save the latter case, the primary injury is to the parenchyma and, even in the latter, the inflammatory reaction in the portal tracts, consequent upon the cholangitis, is associated with secondary changes in the periportal parenchyma. A relationship between parenchymal degeneration and the development of fibrous tissue in the liver is suggested by the work of Cameron and Oakley.[12] They showed that transplants of normal liver provoked a fibrous reaction in the surrounding tissues, although transplants of boiled liver did not. As degeneration occurs in the parenchymal cells of both types of transplant it appears that, on the death of the unboiled cells, some substance is liberated which causes fibrosis to develop.

Hepatic fibroses fall into two anatomical types, post-necrotic scarring and diffuse hepatic fibrosis. Post-necrotic scarring occurs only after the massive types of hepatic necrosis. At the site of the lesion the dead cells are removed; a conspicuous inflammatory reaction occurs, the reticulin net collapses (Fig. 4) and can be seen slowly to mature into collagen fibrils. It is, however, noteworthy that the development of fibrosis after massive necrosis is somewhat tardy,

sequences of hepatic injury are determined by the anatomical form of the lesion,
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between massive and zonal hepatic necrosis is drawn.

Regeneration following Injury

The capacity of the parenchymal cells to proliferate is astonishing. In respect of normal liver tissue it has been established that after removal of 70% of the liver from a healthy animal, the remnant grew so that two to three weeks later the animal again possessed the amount of liver substance appropriate to its size.[41, 46, 53] In zonal necrosis three-quarters of every lobule may be dead; yet in a fortnight the liver may have been reconstituted. And in massive necrosis similar

to proliferate upon the remaining parenchyma, and it is important to consider the factors which determine and influence this process.

Proliferation following injury proceeds rapidly until the mass of parenchymal tissue approximates to the normal. It then stops. In the case of a zonal necrosis the explanation might well be that proliferation continued until the vacant spaces in the reticulin net were filled by new parenchymal cells. But such an explanation could not apply to the hypertrophy of the liver remnant after partial hepatectomy, or partial atrophy (Fig. 10) or to the hyperplasia of isolated groups of cells in areas affected by massive necrosis. There a structure is produced which cannot be related to pre-existing anatomical considerations The most plausible explanation of this controlled process is that the proliferation is in the nature of a work hypertrophy regulated by the functional demands on the liver

This proliferation in response to reduction of parenchymal tissue can only occur under appropriate conditions Mann[42, 43, 44, 45] found that regeneration does not occur in partially hepatectomised dogs if the portal vein is constricted. This is in accord with other work showing that diversion of the portal blood-flow through an Eck fistula causes atrophy of the normal liver[44, 53] and that ligation of one of the two main branches of the portal vein leads to atrophy of the lobes it serves and concomitant hypertrophy of the other lobes whose blood



Fig 7—Post-necrotic scarring The left half of the section has been previously affected by massive necrosis and is now represented by scar tissue The right half of the section is unaffected, there is no excess of fibrous tissue and the portal tracts and hepatic veins are entirely normal. Rat. Low protein diet Laidlaw's reticulin stain × 25

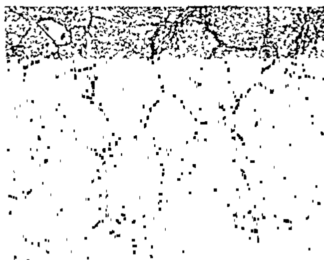


Fig 8—Diffuse hepatic fibrosis. Early stage Laidlaw's reticulin stain Fine bands of connective tissue permeate the liver linking up the portal tracts and hepatic veins The process is uniform so that no normal portal tracts or hepatic veins survive Rat High fat, moderate protein diet. × 25

an observation which can perhaps be related to the affected sites being speedily cleared of degenerating parenchymal cells. In post-necrotic scarring the fibrosis is limited to the areas of previous necrosis, while those, which were unaffected, survive unaltered (Fig. 7). The final result is an organ cut into by coarse bands of fibrous tissue which separate areas composed of entirely normal liver lobules (Fig. 5).



FIG 5—Post-necrotic scarring showing the deep and irregular scars separating normal liver tissue Rat Low protein diet Natural size (The left half of the middle lobe has been cut away to show the scarring in the left lobe)

Diffuse hepatic fibrosis, in contrast to post-necrotic scarring, is distinguished by a fine fibrosis throughout the whole organ so that the liver, instead of being distorted and nodular, shows a uniform granularity (Fig 6). The lesion develops insidiously and, in the case of post-infiltrative diffuse hepatic fibrosis, without preceding necrosis

as a thickening of

or central veins.

other so that eventually, throughout the whole liver, there develops a fine fibrous network isolating and intersecting the individual lobules (Fig. 8). Every lobule is involved; there are no isolated areas where normal lobules survive intact; neither normal portal tracts nor normal hepatic veins are found once the lesion is established This type of hepatic fibrosis is seen after fatty infiltration, repeated frequent attacks of zonal necrosis and following biliary obstruction.



FIG 6—Diffuse hepatic fibrosis The liver is uniformly covered with fine granulations, some of which are projecting and showing hyperplasia Rat High fat, moderate protein diet Natural size

The diffuse fibrosis after

parts of the organ as a whole; but at each post-necrotic scarring inevitably results. Diffuse hepatic fibrosis, on the other hand, is essen-



FIG 9—Zonal centrilobular necrosis Portal tract showing inflammatory reaction although the parenchymal cells round it are unaffected by the necrosis. Rat Subcutaneous injection of carbon tetrachloride Haematoxylin and eosin × 480

tially the result of a chronic process [illegible]

are separated by intervals of ten days or a fortnight, single attacks of centrilobular necrosis occur, each clearing completely before the advent of the next If, however, the injections are given at shorter intervals, diffuse hepatic fibrosis appears The permanency and development of this depends upon the injections being continued. Stop the injections at the first sign of fibrosis and resolution occurs; continue them until the fibrosis is well established and then, even on stopping the injections, the fibrosis continues to develop until the animal dies. It appears as if a high [illegible]

provided the stimulus to its production is in abeyance[9]

It thus seems that fibrosis, like regeneration, must be included in

infiltration, or repeated zonal necrosis, involves both portal tracts and hepatic veins and there is, as yet, some disagreement as whether the process begins in the former or the latter.[2a] This is not surprising, as it is difficult to distinguish an hepatic vein, around which fibrosis is occurring, from a portal tract. If, however, the portal tracts are marked by injecting the bile ducts with Indian ink, the distinction can be made with certainty, and it then appears that the process may commence at either place, but that, shortly, both are involved. But this distinction can only be made at an early stage for soon new bile ducts grow down the newly-formed fibrous bands to the central veins. It then becomes impossible to distinguish these as such for each nodal point in the network of fibrosis resembles a portal tract.[2a, 27a] To this fact, and not to any irrefutable evidence that the condition is primarily a lesion of the portal tracts, may be attributed the traditional designation of the lesion as 'portal' cirrhosis.

Now it is easy to understand the development of fibrosis around the portal tracts when the parenchymal lesion is periportal; or around the

more difficult to understand the fibrous reaction which occurs in the portal tracts when, as in the case of repeated poisoning with carbon tetrachloride, the necrosis is centrilobular. Recent work, however, throws some light on this problem. Gillman[23] has described a fatty infiltration of the liver, prevalent in South Africa, in which iron pigment appears in the parenchymal cells. In time these degenerate and the pigment, thus liberated, finds its way to the adjoining portal tracts where fibrosis develops Similarly, in animals, when centrilobular necrosis has been produced by carbon tetrachloride a cellular reaction occurs in the portal tracts (Fig. 9) It is thus evident that in some way, as yet unexplained, products of cellular degeneration can pass from within the hepatic lobule to the portal tracts at its periphery and provoke a fibrous reaction

[1] The diffuse hepatic fibrosis following biliary obstructions is distinguished by the fibrotic process being centred on, and often confined to, the portal tracts. Even in old standing cases entirely normal hepatic *veins can still be distinguished (Fig. 57). The combination of inflammatory* reaction in the portal tracts and degeneration of the periportal parenchyma adequately explains its pathogenesis.

[2] Post-necrotic scarring is the result of a single attack of acute massive necrosis. Several such injuries may occur at different times in different

of the spleen. In the past such splenomegalies were considered to be caused by portal hypertension secondary to obstruction to the blood-flow by the diseased liver. While this factor undoubtedly plays a part in many, it cannot be the sole explanation of every case for there is no accurate correlation between splenomegaly and the one equivocal

In man the splenic enlargement takes some months to develop and, therefore, is not seen in acute necrosis, cases of which either die or recover in a matter of weeks. It is, however, a conspicuous feature in patients with a subacute necrosis surviving for more than a year, whether the subacute lesion is the sequel to an acute necrosis or the result of a continuing infection such as occurs from a cholangitis secondary to biliary obstructions In the spleens of these cases hyperplasia of the reticulum occurs and it is perhaps relevant to note that in many there is also widespread enlargement of lymph glands showing a similar hyperplasia. McMichael[29] first suggested that the spleen might stand in relation to the liver as lymph glands do to other structures,

Sarum[13] who showed that the reticular hyperplasia and the splenic enlargement, associated with the diffuse hepatic fibrosis following

system severed

portal hypertension, and a toxic factor, derived from the degenerating liver cells, which causes hyperplasia of reticulum cells.

Injuries consequent upon Degeneration

From a consideration of the damage wrought by zonal and by massive necrosis, the conclusion was reached that complete recovery after a single attack of necrosis depends upon the preservation of the

the category of automatic, non-specific reactions of the liver to injury. The composite picture resulting from these two reactions, fibrosis

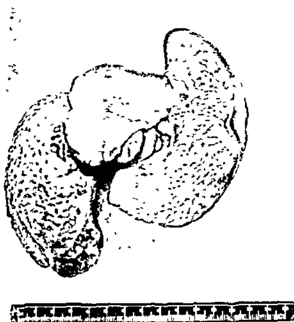


Fig 10—Hypertrophy of the right lobe of the liver following atrophy due to diffuse hepatic fibrosis of the middle and left lobes The right lobe is eight times as large as normal Rabbit 2% cholesterol, high fat diet

associated with parenchymal regeneration, comprises the hallmarks of 'cirrhosis of the liver'. It is evident, however, that it is in no way a characteristic response to a specific cause. It is simply the normal reaction of the liver to injury whatever the cause of that injury.

Splenomegaly as a consequence of Liver Injury

The association of splenic enlargement and lesions of the liver is such a common finding as to merit discussion Disregarding for the present the simultaneous enlargements of the two organs due to involvements of the reticulo-endothelial tissues common to both, and

as a medium in which connective tissue fibrils are formed from the exuded plasma proteins. Serous inflammation is, therefore, regarded as a major factor in the production of chronic disease of the liver. Other workers, however, have not attached the same importance to the phenomenon, regarding it as little more than a simple oedema,[25, 28] and indeed, Eppinger himself, despite the stress he lays on the condition, admits that permanent damage does not occur, unless the reticulin framework of the lobules is also disrupted

The Factors Producing Liver Damage

From the brief survey which has now been made of the types of liver injury and their sequelae, the general conclusion emerges that the outcome of any injury is determined by reactions inherent in the liver itself rather than by the nature of the injurious agent. The types of chronic liver diseases are thus related, not to their causative agents, but to the form of the initial injury. Unfortunately, as we have seen, such initial injuries are not usually characteristic of the factors causing them It is clearly impossible, therefore, to classify lesions of the liver on an aetiological basis What is possible, however, is to classify the various factors which may injure the liver and to indicate the form of lesion which they commonly produce From a knowledge of the train of events initiated by particular lesions the probable results of exposure to particular injuries can then be inferred The following classification of such factors is tentatively suggested·

Vascular Factors
Nutritional Factors
Metabolic Factors
Noxious Factors
Biliary Factors

In the ensuing chapters the way by which these lead to liver injury, and the circumstances which determine the type of injury produced, will be examined

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reticulin framework and the survival of a rim of parenchymal cells in each lobule. It is evident that in acute and transient degenerations, which fall short of cellular death, these conditions are both satisfied and, as would be expected, such lesions do not lead to permanent changes in the liver structure. But in chronic degenerations which exist for many months or years, permanent changes sooner or later appear, a diffuse hepatic fibrosis insidiously develops. Such fibroses appear after long-standing fatty infiltration, in glycogen disease and in those conditions in which the Kupfer cells, and usually many of the parenchymal cells, are choked with substances, such as cholesterol or phospho-lipoids, which *are not normally present* save in small

Injuries consequent upon Focal Inflammation

The generalizations regarding factors which determine whether complete recovery or permanent damage shall follow hepatic necrosis are also relevant to a consideration of inflammation in the liver. In focal inflammation, such as gummata, parenchymal cells and reticulin net are destroyed over a wide area at the site of the lesion. Inevitably a local scar results. If, however, the foci of inflammation are smaller, as in the focal necroses of typhoid fever, and neither disrupt the reticulin nor kill whole lobules of parenchyma then, after subsidence of the inflammatory process, complete restitution of the normal lobule occurs. In persistent chronic inflammation of the portal tracts arising from a cholangitis, the cells in the periportal zone are continually being killed and circumstances are similar to those in experiments where frequent attacks of zonal necrosis are produced. Here, however, *another factor probably plays its part; the direct inflammation* of the connective tissues of the portal tracts. The result is a diffuse type of hepatic fibrosis.

The general problem of inflammation of the liver cannot be left, however, without reference to the concept of serous inflammation evolved by Roessle[47] and developed at length, and particularly in regard to the liver, by Eppinger.[19] Serous inflammation is envisaged as a condition in which there is increased capillary permeability.

CHAPTER II

THE VASCULAR FACTOR IN LIVER INJURY

AN invariable and striking feature of the circulatory arrangements in vertebrates is that the liver receives a double blood supply, venous blood through the portal vein and arterial blood through the hepatic artery This unusual feature is reproduced so consistently in such widely diverse species as to suggest that it has a special functional significance. That it has an anatomical significance is evident. Examination of the normal liver shows that it is constructed in relation to its vascular trees[31, 49, 51, 63, 77] Consideration of the alterations in shape and size of the diseased organ resulting from local interference with its blood supply, and of the alterations which occur after birth, when the foetal gives place to the adult circulation,[5] reveal clearly that the gross form of the liver is determined by the arrangement of its vascular supply. But such alterations in gross form rest on changes in minute structure, and it is in the vascular relationships of the hepatic parenchyma that their explanation must be sought

The classical conception of the liver lobule, put forward by Kiernan[51] over a hundred years ago, was built round the centrilobular vein Later Sabourin[77] attempted to orientate its arrangement to the bile

dimensional view of the liver obtained from transverse sections, and that when the liver is examined in bulk the parenchyma is found to be arranged, not in lobular units, but in the form of a continuous wrapping to the interlocking afferent and efferent vascular trees throughout their lengths[49, 63] The modern tendency, therefore, is to orientate the arrangement of the hepatic parenchyma, lobule or column, to the portal tracts and in particular to its blood vessels

It is generally accepted that in the normal organ there is no direct connection between the efferent and afferent vessels of the liver. In every case blood brought to the liver, whether by artery or by vein, must traverse the sinusoids between the cords of parenchymal cells before reaching the hepatic veins and flowing out of the organ It is similarly accepted that blood conveyed by the portal vein is delivered directly into these sinusoids. What is not completely agreed is the

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supply, which in the space of three months can increase from being but one-fifth of the liver to the size of the normal organ. Comparable



Fig 11



Fig 12

[illegible] with ulcerative colitis Well marked cen- [illegible]

[illegible] Coronary thrombosis 3½ weeks before death At autopsy the right half of the liver showed the 'nutmeg' changes of cardiac failure, the left was atrophic An organizing thrombus was found in the left branch of the portal vein Section from the left lobe of the liver The only surviving parenchymal cells are round the portal tracts The liver is atrophied as shown by the microscopic field containing six portal tracts when at most it should have contained two or three H and E × 65

results occur in the human liver Figure 12 shows the effects of a long-standing thrombosis of the left branch of the portal vein and the appearance is identical with that obtained by Rous and Larimore[26] [illegible] Baum- [illegible] with- [illegible] rough the falciform ligament connecting the portal and systematic venous systems If, as is maintained, the large vein in the falciform ligament is

destination of the hepatic artery. Originally, it was thought[21] that the hepatic artery had no direct connection with the sinusoids but broke up, in the portal tracts, into a capillary net, the venous efferents from which drained into the sinusoids. Later, evidence was found that such direct connections did exist[49, 70, 89] and, at present, the general view is that the hepatic artery is distributed in both these ways.

OBSTRUCTION OF THE HEPATIC VESSELS

It is a constant observation that the liver dies when it is totally deprived of its blood supply, but the effects of obstructing the individual hepatic vessels are inconstant, varying both from species to species and between animals in the same species. Nevertheless it is possible, not only to distinguish a broad pattern in these effects but also to explain the various discrepancies in the light of the conditions under which they are produced

Portal Vein

Sudden complete obstruction to the portal flow into the liver leads within a short space of time to death from paralysis of, and haemorrhage into, the intestines The uncomplicated effects of total deprivation of the portal supply can, therefore, only be studied when obstruction is confined to one of the main branches of the portal vein. These effects were clearly defined by Solowieff[84] in 1875 as atrophy of the parenchyma and 'fibrosis' in the affected part. No conspicuous necrosis occurs Essentially the same results have been obtained by later workers[4, 62, 76] and also by those who have studied dogs in which the portal inflow has been reduced by an Eck fistula[64, 66, 91, 92] The later work has, however, clarified two further points. First, that the so-called fibrosis is not due to increase of connective tissue but to agglomeration of the portal tracts after disappearance of the parenchyma. Second, that although the bulk of parenchyma commonly vanishes without obvious necrosis, antecedent changes are evident in the cells and these, as is the case in the infrequent frank necrosis (Fig. 11),[82] are most marked in the centrilobular zone

The extent to which the parenchymal atrophy progresses is astonishing. Thus in the rabbit, three months after occlusion of that branch of the portal vein supplying two-thirds of the liver, there remains but a fibrous tag consisting of bile ducts, blood vessels, fibrous tissue, and a few surviving parenchymal cells. And equally remarkable is the hypertrophy, occurring in that portion of the liver with an intact portal

care to base their observations on animals in which they judged the collateral circulation was not excessive, it is clear that a condition, providing for the circumvention of the obstruction to the portal vein, was in course of development, and that such circumvention, when present, could account for their results and render unnecessary the new hypothesis which they put forward.

These conditions are very relevant to the interpretation of portal vascular disease in man There, portal thrombosis usually occurs secondarily to chronic sclerosing conditions of the vessel. This impedes portal blood-flow and promotes the development of collateral vessels capable of immediately taking over the flow of blood when thrombosis obstructs the original channel As a result, the majority of such cases show no parenchymal lesions. Such lesions are only found in man in those rare cases in which acute thrombosis occurs before venous collaterals have developed or involves a vessel close to the liver and beyond the site at which adequate side channels can arise. In such cases the results of ligation in animals are duplicated (Figs. 11 and 12).

Hepatic Artery

The effect of collateral channels in mitigating the hepatic lesions produced by occlusion is of even more importance in relation to

been established in rabbits.[9, 21, 24, 42, 52] cats,[4, 9, 20, 42] and dogs.[42, 53] The

the liver

In man comparable results are only found in cases where sudden obstruction has occluded a hitherto normal vessel at a site near the liver. In the majority of human cases such conditions do not apply, for chronic

accidental ligation of the artery[47, 50, 69, 78] has occurred to establish that *necrosis follows.*

The discrepancies between the results of ligation of the portal vein in different species was seen to be, in part, related to the dependence of the hepatic parenchyma in that particular species on the portal

a persistent umbilical vein, then such cases would be comparable to animals with Eck fistulae, and the atrophic fibrosis of the liver may be the result rather than the cause of the collateral circulation.

But discrepancies from this general picture of atrophy without necrosis do occur and require explanation McMichael[82] threw [illegible]

[illegible]

infrequently does so in cats, whose portal blood contains more oxygen. Again, in shocked animals the lesions are more severe than in those in [illegible]

[illegible]

therefore, to be related in the particular animal, to the normal dependence of the parenchymal cells upon the portal inflow for their oxygen

That adequate collaterals by-passing the site of obstruction would mitigate, or even prevent, a lesion is evident and it is also clear that, as investigators came to realize this point and took more care in the placing of their ligatures, the number of experiments in which no hepatic lesions were produced steadily diminished Many discrepant results are explicable on these grounds, but particular consideration need only be given to one which, because its explanation required the enunciation of a new principle in pathology, deserves special attention.

In accordance with general experience Rous and Larimore[78] found *that after ligation of one branch of the portal vein the liver served by* that branch atrophied while the rest hypertrophied (cf. Fig. 10) If, however, at the time of ligation of the portal branch, they also ligated the bile ducts to the other lobes, whose portal blood-flow was uninterrupted, hypertrophy did not occur in these lobes and the atrophy, which normally occurs in the lobes deprived of portal blood was either absent or inconspicuous. They interpret these results to mean that the atrophy, consequent upon local deprivation of portal blood, is conditional upon hypertrophy occurring in the rest of the liver. On examination of the details of their experiments, however, a simpler explanation suggests itself. Ligation of the bile duct produced numerous necroses in the affected lobes and resulted in the rapid development of a 'biliary cirrhosis'. This evidently impeded the portal circulation, for soon unequivocal signs of portal hypertension appeared in the form of congestion of the intestines and the development of numerous venous collaterals. Although the investigators took

the centre of the lobule As long, however, as the flow of blood through the liver is not reversed, the intravascular pressure must





Fig 13 Fig 14

Fig 13—Congestive cardiac failure 'Nutmeg liver' Mild case, showing degeneration confined to the centre of the lobule H and E × 65

Fig 14—Congestive cardiac failure 'Nutmeg liver' Advanced case The only surviving parenchymal cells are round the portal tracts, indicating that survival depends upon proximity to the inflowing blood H and E × 65

necessarily be higher in the neighbourhood of the portal tracts, where the cells are healthy, than in the centre of the lobule, where the cells are dying. These considerations bring the phenomena after obstruction to the outflow of blood from the liver into line with those observed after the restriction of the inflow Obstruction to the outflow seems to produce its effects simply by impeding the inflow of blood into the lobule

The final consequences of such obstruction are those which would be anticipated from the anatomical form of the initial lesion The commonest result is a diffuse hepatic fibrosis which is in no way extraordinary save that there is a tendency for the fibrosis round the central

blood for its oxygen supply. Investigation of the results of portal ligation, in relation to those of ligation of the hepatic artery in the same species, shows that some animals rely more on the portal blood for oxygen, others on the arterial blood.[62] In those which rely mainly on the latter, ligation of the vein has little, but ligation of the artery a profound effect. This reciprocal relationship is not only adjusted differently in different species but is readjusted in the same species according to the state of the general circulation. As the blood pressure falls the liver comes to depend more and more upon its

the arterial inflow, are primarily dependent upon the extent to which the total blood-flow to the liver is curtailed. The common destination of both the arterial and venous inflows is the intralobular circulation, and when this becomes inadequate, either quantitatively or qualitatively, a parenchymal lesion results. The extent of this varies with the severity of the ischaemia, but, initially, it is centrilobular in type.

Hepatic Veins

Experimentally, partial obstruction to the outflow of blood from the liver speedily results in a centrilobular necrosis of the parenchymal cells,[11, 12, 81, 82] which is followed by a fibrosis of the liver especially marked round the central veins. A comparable condition occurs clinically in Chiari's syndrome[23] of obliterating endophlebitis of the hepatic veins[2, 45, 50, 68] In this also the immediate lesion is a centrilobular necrosis and the ultimate lesion hepatic fibrosis. Of more importance, however, is the familiar 'nutmeg liver'[51] which commonly occurs in congestive cardiac failure and in the less frequent condition of constrictive pericarditis. In these the immediate obstruction to the outflow from the liver is functional rather than structural, being due to high pressure within the inferior vena cava. But the effects are the same. In mild cases lesions are seen in the centre of each hepatic lobule. Here the liver cells have disappeared, or are disintegrating after necrosis,[12] and the sinusoids are widely dilated (Fig 13) When the condition

but equidistant from the portal tracts whence comes the nutri-
explain this
pressure in

by Copher and Dick[83] who showed, by injecting dye into the splenic or superior mesenteric vein, that the currents from these vessels kept to the left and right respectively in the portal vein. As a consequence of the arrangement, blood from the intestine passes mainly up the right branch of the portal vein to the right lobes, while that from the spleen proceeds by the left branch to the left lobes That this is a genuine and consistent occurrence and not merely an artefact produced in an acute experiment, is shown by the observation that if the spleen is repeatedly injected with carbon tetrachloride then a hepatic fibrosis confined to the left lobes of the organ develops.[85]

But it is particularly in regard to dietetic massive necrosis that these observations have proved of value. When rats are given a diet completely deficient in one respect, then massive necrosis ultimately *develops in the whole liver. If, however, the diet is partially inadequate*

to test this hypothesis Indian ink was injected into the spleens of normal rats The ink passed at once to exactly those parts of the liver commonly affected by partial necrosis (Fig. 15). It was more difficult to demonstrate that the right lobes received blood from the superior mesenteric vein for the ink must be directly injected into the vessel and the force of injection, being unbuffered by any structure like the splenic pulp, tends to disturb the stream-lines and throw the ink to all parts of



FIG 15—Vascular territories in the liver 0·2 c c of

size

veins to be more pronounced than in other types of diffuse fibrosis.[48] Regeneration nodules do occur, but they are not common, and this is not surprising in that the lesion is essentially due to curtailing the supply of nutriments to the parenchymal cells. Fibroses due to congestion are, however, of slow development. Only a minority of cases of congestive cardiac failure, with the requisite degree of congestion, survive long enough for their production. Patients with constrictive pericardities, however, frequently survive for the necessary time, and in these fibrosis of the liver is a more constant finding.

Thus all the evidence derived from a study of the effects of obstruction to the various hepatic vessels points in one direction; that the hepatic parenchyma is orientated to, and dependent upon, an inflow of blood of appropriate composition. The results of interference with any one of the vessels is determined by the extent to which, in particular circumstances, it impairs the intralobular circulation. The interference may be compensated either by the development of collateral channels or by reciprocal augmentation of the flow from other sources, but, if adequate compensation does not occur, parenchymal degeneration follows. This commences in the centrilobular zone, but in some cases it may extend to become massive in form. Its ultimate results are determined, as in other types of necrosis, by the anatomical form it finally assumes.

LOCAL VARIATIONS IN THE INTRAHEPATIC CIRCULATION

Examination of massive necrotic lesions in the liver shows that they [illegible] e of the [illegible] onform [illegible] viscus or overlapping lobe. But this explanation can only account for a minority and in particular it fails to account for that predilection of massive necrosis for the left lobes of the liver which has been observed in animals[39 46] (Fig 16) and which was remarked in man long ago by Rokitansky,[73] and has since been confirmed by numerous observers[10 34 54] (Fig. 45)

Stream-line effects in the portal vein

Glenard[33] was the first to suggest that different parts of the liver received blood from different regions of the alimentary tract and

CHANGES IN THE INTERNAL ENVIRONMENT OF THE PARENCHYMA DUE TO CIRCULATORY OBSTRUCTION

Anoxia

It has already been remarked that an invariable feature of the circulatory arrangement in vertebrates is that the liver is supplied with both venous and arterial blood and observations have been cited which show that, in the absence of arterial blood, necrosis rapidly occurs It is evident, therefore, that an essential factor for the normal metabolism of parenchymal tissue is supplied by arterial and not by venous blood. The most obvious difference between the two is in respect of oxygen, arterial blood containing oxygen not only in greater amounts, but [illegible]

necrosis is produced A similar lesion has also been observed when the oxygen supply to the liver is diminished by circulatory failure.[62]

But, anoxia is a relative term If the needs of the tissue are elevated then blood with an oxygen saturation, which would suffice under ordinary circumstances, may prove quite inadequate Such is the state in hyperthyroidism. Thyroxine increases the oxygen requirements of the liver [72] and, according to some, but not to all, workers, rats injected with thyroxine develop centrilobular necrosis even when living in ordinary air [32 36 41 43] Certainly, in such animals, centrilobular lesions appear on exposure to slightly reduced oxygen tensions which are entirely without effect upon animals not injected with thyroxine In man, liver lesions are common in hyperthyroidism [7 18 59 90] In acute cases these range from centrilobular fatty change, or necrosis, to massive necrosis of the liver, and chronic cases show the corresponding sequelae of diffuse hepatic fibrosis and nodular hyperplasia. It would be rash, however, to conclude that the human lesions were entirely the result of relative anoxia On the analogy of the experimental results this factor probably plays its part [illegible]

elevation [illegible]

may well [illegible]

of dietetic necrosis, suggests that a relative deficiency of essential nutriments may be a significant factor in their production It is clear, however, that oxygen lack, whether due to a deficient supply, as in exposure to low pressures of oxygen or circulatory failure, or to

the liver But it has been done and the distribution of blood from the small intestine to the right lobes confirmed. It is thus evident



FIG 16—Partial massive hepatic necrosis Rats Low protein diet From left to right, acute massive necrosis, subacute massive necrosis, post-necrotic scarring The lesion is confined to the left lobes of the liver, sparing those areas which receive blood from the small intestine Natural size

that partial, massive, dietetic necrosis develops in these areas of the liver which normally receive splenic blood or, to put it another way, such necrosis does not develop in those areas receiving blood from the small intestine. The inference is clear. Dietetic necrosis is a disease due to a nutritional deficiency; digestion occurs in the small intestine; its products are carried in the blood of the superior mesenteric vein which supplies the right lobes of the liver. When the diet is adequate, the amount of the essential nutrient in the portal blood is high and sufficient escapes through the liver to reach the arterial blood and so nourish the left lobes. When, however, the diet is partly deficient most of the nutriment is removed by the right lobes, inadequate amounts get through to the left, and ultimately massive necrosis develops there.

It is, perhaps, of significance that no such differences in distribution of the hepatic arterial flow have been demonstrated. The partial dissociation of the liver into two vascular territories seems to be mainly confined to the portal system, and in that system it is evident that local anatomical factors, and external agents, such as pressure, produce alterations in circulation of potential significance

blood. Such a factor, presumably, is supplied in the territory drained by the portal vein It might well be a product of digestion.

Severe and mild deprivations

The foregoing considerations have tended to relate acute necrosis to anoxia and slow atrophy to deficiency of other nutriments. It would not, however, be justifiable to conclude that this is invariably the case. Dietary deficiencies are associated with hepatic necroses as severe as those due to anoxia,[39,46] and it is at least possible that minor degrees of oxygen deficiency may lead to atrophy. The difference seems to be principally one of degree, sudden and severe deficiency of either factor resulting in an acute degeneration, necrosis; prolonged but less severe restriction in atrophy. Circulatory disturbances, however, more readily produce acute anoxia than acute nutritional deficiency, for the parenchyma is immediately dependent for its oxygen upon the circulating blood while it contains within itself reserves of food which can sustain it during acute ischaemia.

DERANGEMENTS OF THE CIRCULATION IN THE DISEASED LIVER AND THEIR CONSEQUENCES

The prese[illegible]

supplies of [illegible]

The occurre [illegible]

that deficiency of an essential nutrient may exist only in one part of the liver, and the relationship of that lesion to the distribution of the inflowing blood indicates that differences in the circulation within the liver may lead to grave local damage. Such local differences frequently arise in disease and, if they occur with any consistency in a particular [illegible]

[illegible] deficiencies and, as the composition of the blood differs in different parts of the intrahepatic circulation, the site of the circulatory disturbances can often be inferred. Clearly, however, such inferences are only possible when the blood flowing to the liver is normal in composition If it is impoverished in any respect, lesions may arise without any disturbances of the intrahepatic circulation or from such minor disturbances as would ordinarily have no effect.

increased demands by the liver parenchyma leads to necrosis of the liver which is centrilobular in type.

The question now arises as to whether the amount or tension of [illegible]

failure, hepatic necrosis has not been remarked. On the other hand exposure of animals to tensions less than one-third of that in air has produced hepatic lesions although the amount of oxygen in the blood of such animals is far greater than in many anaemic persons. Again, if the amount of available oxygen in the blood flowing into the liver were the essential factor, then it would be expected that the liver would remove approximately the same amount of oxygen whatever the level of oxygen saturation in the inflowing blood. If, however, the important factor were the tension of oxygen in the blood then the amount removed should be proportional to the particular tension. McMichael's [62] results support the latter supposition. It appears, therefore, that an essential function of the blood supply to the liver is to provide oxygen for the parenchymal cells at a sufficiently high tension. The portal blood being partly reduced, the necessity for providing an arterial inflow to augment its oxygen tension is apparent. The reason for the existence of a hepatic artery is thus comprehensible.

Deprivation of Components of the Portal Blood

When the oxygen supply of the liver is adequate, sudden and complete deprivation [illegible]

hepatic parenchy

affected (Fig 12)

A high oxygen

to the part was

chymal tissue. If this were so, however, exposure of animals to atmospheres of pure oxygen should produce liver lesions. And it does not. Under ordinary circumstances the portal blood supplies 60% to 80% of the total oxygen requirements of the liver.[62] Deprivation of such amounts of oxygen, while insufficient to cause acute necrosis, might lead to chronic atrophy of the parenchyma But in this case the parenchyma should not almost completely disappear, for the 20% to 40% of the total oxygen requirements supplied by the hepatic artery should ensure the survival of a considerable proportion. It seems, therefore, probable that portal blood contains some factor essential for the nutrition of the parenchymal tissue which is absent from arterial

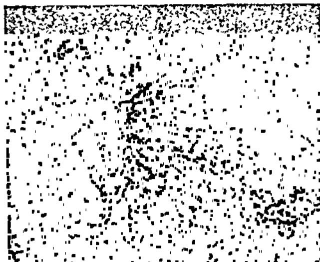


Fig 17—Confluent centrilobular zonal necrosis Rat Subcutaneous injection of carbon tetrachloride, 0 2 c c /100 g body weight The surviving cells are those in proximity to the portal tracts and the zone of survival extends for an equal distance from the tract even when, as in this case, the shape of the latter is irregular (cf Fig 1) H and E × 72

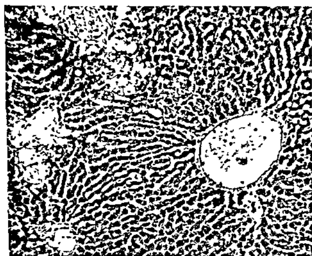


Fig 18—Periportal zonal necrosis Rat Subcutaneous injection of the endotoxin of Proteus vulgaris Note the widely dilated sinusoids and hepatic vein H and E × 72

Centrilobular and Periportal Zonal Necrosis

One of the most puzzling observations in pathology is the centrilobular necrosis which follows subcutaneous injection of moderate doses of carbon tetrachloride. It is known that the liver rapidly absorbs this substance from the blood,[20] yet those cells which are necessarily exposed to it in the highest concentration, the periportal cells, survive while those less exposed to its action, the centrilobular cells, become necrotic (Fig 1). When, however, large doses are given, a significant extension of the lesion may be observed. The necrotic areas are no longer confined to the centrilobular region but have joined together to isolate the portal tracts, round each of which survives a cuff of parenchyma of uniform thickness, accurately moulding the irregularities in shape of the particular tract (Fig 17). It is evident that the necrosis has only occurred in those cells which are distant from the portal tracts, an observation which suggests that survival is dependent upon proximity to the lobular blood supply. It would be expected, therefore, that the necrotic lesion would be more severe in animals whose blood has been depleted of those substances on which the parenchyma is dependent And it has been found, after injection of carbon tetrachloride, that rats exposed to low oxygen tensions show far more severe lesions than the control animals in air.[464] Comparable results have been observed after administration of divinyl ether and chloroform, and it has further been shown that the centrilobular necrosis normally produced by these substances is mitigated by concurrent administration of oxygen.[49] Of similar import is the observation that thyroxine, which increases the demands for oxygen, increases the severity of the hepatic lesion due to chloroform.[58, 60] It is therefore evident that the oxygen supply to the lobule is an important factor in the production and localization of the necrosis due to the chlorinated hydrocarbons. There are two possible explanations of this: either oxygen is necessary for detoxication of the poison, or the observed necrosis is the result, not of direct toxic action, but of deprivation of oxygen. Such a deprivation might well be the result of ischaemia and there is good experimental evidence that exposure to the chlorinated hydrocarbons is followed by marked restriction of the intralobular circulation.

Observing the rat's liver directly by transmitted light Loeffler and Nordmann [534] found that, some hours after administration of chloroform the intralobular sinusoids were greatly narrowed. This they attributed to a reflex constriction Using a similar technique Wakim and Mann [68] observed that the sinusoids were practically obliterated

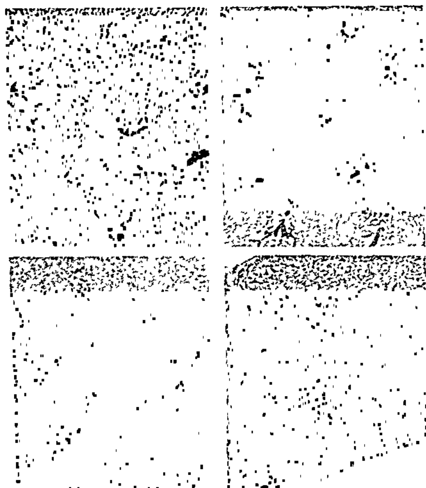


Fig
liver ce
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A (
subcutaneous injection of 0·2 c c /100 g body This is in conspicuous contrast to a
greatly reduced in diameter, blood uniformly involves the whole organ In the gross
reaches the hepatic veins C necrosis are sharply demarcated from the healthy liver
are not visible, the necrosis and have a general predilection for the left lobes of the organ
the portal
fined
(Fig. 16) Microscopically the demarcation may be sharp so that there

eight hours after exposure to carbon tetrachloride vapour. At the same time the liver cells were grossly swollen. Direct evidence (Fig. 19) that the intralobular circulation is impeded under such circumstances has been obtained by Glynn and Himsworth[38] and more recently by Andrews.[14]

Carbon tetrachloride is injected subcutaneously into rats and, at intervals afterwards, a fine, filtered suspension of Indian ink is injected into the spleen. The injection passes into the liver and, in the normal animal, fills the intralobular sinusoids, the portal vessels, and the hepatic veins. Two hours after injection of carbon tetrachloride, before centrilobular necrosis has appeared, the parenchymal cells are so swollen that the ink is excluded from, or penetrates only weakly into, the central zone of the lobules while it densely infiltrates the vessels in the portal tracts and the peripheral parts of the intralobular sinusoids. *After degenerative changes have appeared in the centrilobular cells* the exclusion of the injection from the central zones is even more pronounced[38] (Fig. 19). Centrilobular necrosis does not appear, however, until some twelve hours after administration of the carbon tetrachloride and some eight hours after the sinusoids have become narrowed. Eight hours is the period of time required, after ligation of the hepatic artery, for the development of those histological changes we recognize as necrosis. Further, anoxia produces vacuolation in the hepatic parenchymal cells provided that the intralobular circulation is not entirely arrested.[66] Morphologically identical vacuolation of the centrilobular cells is the first sign of degeneration in carbon tetrachloride poisoning.

It thus appears that the centrilobular necrosis, after systemic injection of small doses of the chlorinated hydrocarbons, is due to ischaemia of the centrilobular cells, and perhaps to oxygen lack in particular. Under other conditions, however, deficiency of nutriments may be the operative factor. But the sequence of events is the same in all. While large doses of a noxious factor introduced into the portal system produce direct necrosis, smaller doses or those given into the systemic

lobule it has been largely depleted of those substances necessary to the parenchyma. Necrosis of the centrilobular cells then occurs. Further evidence bearing on this point is provided by studies on poisoning by allyl formate or the endotoxin of Proteus vulgaris. These substances

cause periportal necrosis, the central parenchyma remaining apparently normal.[30 75] The problem is to explain the survival of the central cells, for the periportal necrosis seems explicable on the basis of direct toxic action. The first effect following their injection is wide dilatation of the sinusoids (Fig. 18). At no time are these compressed by swollen parenchymal cells. The circulation through the lobule appears free. That it actually is so is shown by injecting a weak solution of allyl formate and later Indian ink, into the spleen. The ink pours through the affected parts of the liver instead of avoiding them as after a similar or subcutaneous injection of carbon tetrachloride.[38] The blood supply to the central cells is unimpeded. They do not, therefore, become necrotic

Centrilobular necrosis occurs in the majority of the common diseases of the liver. It is seen after poisoning with many synthetic and naturally occurring substances,[3 22 29] it is the typical lesion in infective hepatitis and homologous serum jaundice[27 35] (Fig 43). In each case the lesions are identical. It is suggested that, under ordinary circumstances, the lesion directly due to the particular pathogenic agent is, not necrosis, but swelling of the parenchymal cells; and that this so *impedes the intralobular circulation as to curtail the blood supply to* the parenchyma most distant from the inflow of blood The result is a centrilobular necrosis.† Such a view would explain the occurrence of an identical lesion in inflammation of the liver from many different causes and, as will be seen later, will also explain various complications which are prone to supervene in all.

Focal and Midzonal Necrosis

Focal necroses occur in the midzonal region and may extend round half to two-thirds of this zone, though not so as to form a complete ring.
operative are of common occurrence in autopsy material from human
large doses are particularly apt to occur if the final stages of illness have
produce direct necr ontinued low blood pressure and poor general circula-
system, reaching the liver re limited to a few lobules and can usually be
of the parenchyma This obs al tract. Their distribution can be under-
that by the time the slowly percol the so-called central vein is actually
supplied from one portal

allyl formate or the endotoxin of Proteus vulgaris. These substances

tract, and that blood from several adjoining portal tracts drains into each central vein. The local lesions thus occur towards the periphery of a particular circulatory territory, where the effects of a failing circulation would be most felt. The survival of the cells round the central vein can be attributed to their deriving nourishment from blood draining into that vein from adjoining portal tracts.[178]

Midzonal necrosis, in the sense of a complete ring of necrosis [illegible]

of the lesion After consulting numerous pathologists, both in Europe and America, I have only been able to see a few specimens for which any claim could be made that they showed a complete midzonal necrosis In all save one the midzonal appearance was seen only in a few lobules in the section, the remainder showing varying degrees of incomplete midzonal focal necrosis. In a single section, found for me by Professor Arnold Rich of Baltimore, the lesion seemed to affect all lobules It is apparent, therefore, that a precise midzonal necrosis, if it exists, and is not either an artefact dependent upon vagaries in cutting the section or a transient, intermediate stage in a more extensive lesion, occurs with extreme rarity. Such a lesion could be produced [illegible]

were now deprived of their blood supply.

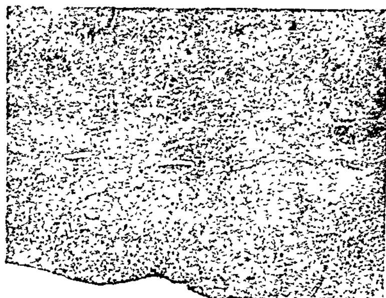
Massive Hepatic Necrosis

Massive hepatic necrosis is also explicable on a circulatory basis This lesion is of two kinds. One is [illegible]

pronounced swelling of the parenchyma in zonal necrosis produced a more nearly complete arrest of the intralobular circulation But the other [illegible]

zonal lesion which uniformly involves the whole organ In the gross the areas of necrosis are sharply demarcated from the healthy liver tissue and have a general predilection for the left lobes of the organ (Fig. 16). Microscopically the demarcation may be sharp so that there

is a precise division between necrotic and living tissue (Fig. 20) In other cases the necrotic area may be bordered by a zone, one or two



sharp line of demarcation of the section all the paren- Rat Low protein diet

lobules deep, where only part of the lobules are damaged. The appearances in this border-line zone are most confusing. Sometimes the intralobular lesion is mainly around the central vein, sometimes haemorrhages occur round the portal tracts, and at others both types of distribution may be found. But in the majority the distribution is so irregular as to be unclassifiable. There are, therefore, many objections to accepting such massive necrosis as a simple exaggeration of a zonal necrosis. Nevertheless its peculiarities are explicable on the basis of circulatory disturbances.

The predilection of dietetic, massive, hepatic necrosis for the left lobes has already been explained by the different blood supply of these lobes. If Indian ink is injected into the spleen of a living animal and its appearance in the liver closely watched, it will be found that the injection appears neither simultaneously, nor in uniform concentration, throughout the whole of the left lobes. In certain areas it appears

quickly and the injection is intense; in others its appearance is delayed and the injection weak (Fig. 21). There is some constancy about this



Fig 21—Showing the irregular distribution of the circulation in the normal liver and the corresponding irregular distribution of massive necrosis Rats Left hepatic lobes Natural size

Left—Normal animal after injection of 0·2 c c Indian ink into the spleen

Right—Partial massive hepatic necrosis Low protein diet

distribution. Areas normally pressed upon by an adjoining viscus or lobe of the liver, and the borders and lower part of the left lobes, take the injection weakly. It seems that the circulation, even within the same lobe of the liver is not uniform. Certain areas are well supplied; others relatively poorly. A peculiarity of dietetic massive necrosis is that, unlike the zonal necroses, which develop in hours or days, it requires weeks of exposure to the necessary conditions before it develops Presumably during the long latent period the particular state of deficiency necessary for the development of the lesion, is slowly being reached in the liver; but it is not until the deficiency reaches a certain level that necrosis appears. It then appears suddenly. Such a state of nutritional deficiency would develop first in areas where the circulation is relati[illegible]
subject to slight, [illegible]
has already been [illegible]
impede the blood supply, and continued over several weeks this may have significant effects

But these considerations do not explain why the necrosis is massive in form, if not at its inception, at least from a very early stage. The

explanation is indicated by the earliest stage of the lesion. At first sight the lesion appears to be limited to the periportal zone with pools of blood round every portal tract (Fig. 22A). But on closer examination it [illegible]
are [illegible]
no [illegible]

As a result blood is dammed back in the vessels of the portal tract and at the entry to the sinusoids. The distension of these latter with blood gives the superficial appearance of periportal haemorrhage. The inevitable result of such a complete arrest of the intralobular circulation is death of all the parenchymal cells within the lobule. The variations in distribution of the necrosis in the borderline zone are explicable by differences in the degree of parenchymal swelling in adjoining lobules whose vascular connections are not entirely separate.

This explanation of the production of this type of massive necrosis is compatible with our knowledge of the affects of anoxia on the hepatic parenchyma It has been shown that anoxia produces parenchymal vacuolation only if some degree of intralobular circulation is maintained [86] This finding has been adduced to support the explanation of centrilobular vacuolation, and subsequent necrosis, which is such a conspicuous feature of carbon tetrachloride poisoning, where *the intralobular circulation is believed to be only impeded. With* complete arrest of that circulation, such as is postulated to occur in the parts affected by dietetic, massive, necrosis, death of the parenchyma without vacuolation would, therefore, be expected. This is actually what is observed

Infiltrations of the Liver

A similar, but much milder, disturbance of intralobular circulation, exists in livers which are heavily infiltrated with such substances as fat. Microscopic examination shows the parenchymal cells, and in some *cases the Kupfer cells, grossly distended and compressing the sinusoids.* Injection of organs in which the infiltration is unequally distributed shows that the Indian ink penetrates less easily into the sinusoids of lobules, which are heavily infiltrated, than into those on which the infiltration is light (Fig. 23). Extensive necroses, however, are seldom



A



B

Fig 22—Periportal haemorrhages in dietetic massive *necrosis* of the liver *Rat* *Low protein, high fat diet* Lesion at the earliest stage of *massive* hepatic necrosis Haemorrhages are present round every portal tract and at places disrupted sinusoids can be seen The parenchymal cells are dead, fusing together, but still *in situ* H and E A × 65 B × 225 The vacuolation in the cells is due to fat globules which had accumulated in the liver consequent upon a high fat diet

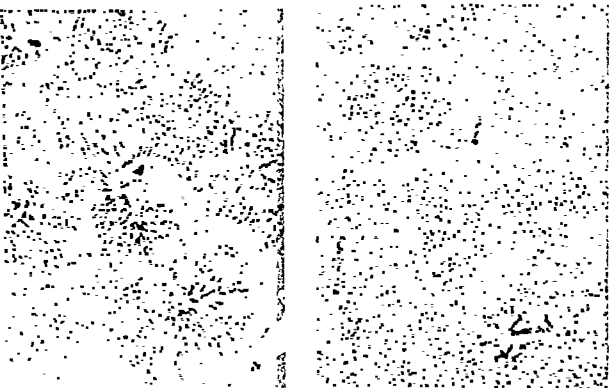


Fig. 23—Showing the restriction of the intralobular circulation consequent upon fatty infiltration of the liver (38) When rats are given a high fat diet then, before the liver becomes uniformly infiltrated with fat, there is a stage at which the fat is irregularly distributed Animals, at this stage, were anaesthetized and Indian ink injected into the spleen The ink avoided the fatty areas The above photographs were taken from different parts of the same lobe of the same liver Frozen sections Scharlach R and haemotoxylin × 80 A, From an area only lightly infiltrated with fat The sinusoids are injected save in the centrilobular zone where the fatty infiltration was heaviest B, From an area more heavily infiltrated with fat The ink is held back at the portal tracts The intralobular sinusoids are not injected

seen under these conditions and it seems likely that the obstruction to the intralobular circulation is insufficient for this purpose. But more chronic types of degeneration, leading to quiet disintegration, are present and are usually first seen round the central vein. It is not suggested that all degeneration in these conditions is entirely due to the circulatory impairment. The actual infiltration of the cytoplasm may itself be deleterious. But the circulatory disturbance at least contributes to the degeneration of the hepatic parenchyma in the centrilobular zone and this, if continued, will lead eventually to the development of diffuse hepatic fibrosis.

Fibrosis

The classical researches of Herrick[44] and McIndoe[57] have demonstrated that gross distortion of the circulation occurs in fibrotic livers. Not only is there a reduction in the total vascular bed but the normal relationships between the different vascular trees are greatly disarranged. As the lobules are destroyed the hepatic veins come into closer relationship to, and finally are incorporated in, the portal tracts so that much of the inflowing blood is short-circuited past the parenchyma. Ultimately the blood vessels are almost confined to the fibrous tissue and are progressively obliterated as this develops into an avascular scar. The development of these alterations of the hepatic circulation has been demonstrated by means of X-ray photographs taken after intracardiac injections of thorium dioxide into animals with hepatic fibrosis due to butter yellow. With such a technique the normal liver appears as a homogeneous shadow, the thorium dioxide being uniformly distributed throughout the lobular sinusoids. After fibrosis has developed, however, the liver appears as a collection of ring shadows and the thorium is confined, almost entirely, to vessels in the bands of fibrous tissue.[85] But such intrahepatic alterations in circulation are not the only ones occurring under these conditions. Outside the fibrotic liver collateral vessels develop and carry much of the portal blood past the organ.

As a result of these changes the parenchymal cells become largely deprived of their supply of portal blood and are ultimately nourished almost entirely by the hepatic artery.[57] The *situation in hepatic fibrosis* thus bears resemblance to that after obstruction to a branch of the portal vein. The effects on the hepatic parenchyma are also similar.

Chronic degeneration leading to atrophy occurs in parts poorly supplied with blood, hyperplasia in the parts where the flow is free. But steadily the amount of fibrous tissue increases and, as this by its contraction constricts more and more vessels, areas of parenchyma hitherto so well supplied with blood as to have become hyperplastic, find their blood supply reduced and in turn degenerate. Thus steadily the process progresses until the amount of parenchyma is reduced below the necessary minimum. Then death occurs.

In the early stages of fibrosis of the liver, this steady sequence is not established. Experimentally this has been demonstrated in fibrosis due to butter yellow,[85] or carbon tetrachloride, and a distinction has been drawn between the reversible and irreversible stages of the condition[19] But once the fibrosis has passed a certain stage, even though the agent that initiated the lesion is no longer operative, the circulatory derangements appear to be such as to ensure its automatic and inevitable further development. Impaired blood supply alone can determine chronicity; and to this may be attributed, in large part, the relentless progress, and ultimately hopeless prognosis, in patients with chronic fibrotic lesions of the liver

THE RELATIVE IMPORTANCE OF CIRCULATORY FACTORS IN THE PATHOGENESIS OF HEPATIC LESIONS

It thus seems that circulatory factors play a large part in determining, not only the course, but the actual appearance of many hepatic lesions. Differences in circulation to the different parts of the liver account for the irregular distribution of certain types of necrosis within the organ as a whole Disturbance of the blood supply by fibrosis may set in train a fatally progressive lesion. Swelling of the parenchymal cells may so interfere with the intralobular circulation as to produce damage Mild swelling, which only slightly restricts the intralobular circulation, leading to quiet degeneration, more marked swelling to a centrilobular necrosis; gross swelling, causing complete arrest of the circulation, to massive necrosis. Thus, in many abnormal conditions of the liver, the lesion which dominates the present state and future course is due, not to the direct and specific action of the pathogenic agent which initiates the illness, but to a secondary phenomenon

consequent upon a non-specific derangement of the intra-hepatic circulation. As such it is essentially a complication, but a complication of such inevitability that, for practical purposes, it can be regarded [illegible]

On occasion the pathogenic agent, either because it is specially virulent or because it is present in unusually high concentration, produces by its direct action on the parenchyma lesions of such severity that death of the cell occurs. In general, however, the primary lesions are surprisingly mild, being often little more than minor degenerations from which recovery is possible. Such occur in many and diverse illnesses Their inevitable effect is a secondary centrilobular lesion whose severity is related to the degree of parenchymal swelling produced by the primary lesion

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CHAPTER III

NUTRITIONAL FACTORS IN LIVER INJURY: EXPERIMENTAL

THE influence of diet in mitigating, or exaggerating, lesions of the liver due to certain poisons has been known for more than thirty years[66] but only recently has it been realized that abnormal diets themselves lead to severe hepatic injury. Looking back it is possible to see that clues pointing to the influence of dietary abnormalities were previously available but, current opinion not being attuned to their significance, their import was missed. As long ago as 1914 Chalatow[17] reported the development of hepatic fibrosis in rabbits given cholesterol in oil for the purpose of producing atherosclerosis, and this observation has been incidentally noted by several subsequent workers[47 56] (Figs. 10, 48). But these results, being produced by the administration of a particular dietary component, in proportions which did not occur in naturally occurring diets, were regarded as toxic effects, and as compatible with the prevailing view which attributed liver injury to the presence of exogenous and noxious substances. It required the demonstration that liver injury could be produced by dietary deficiency for the importance of dietetic factors to be fully appreciated This demonstration was provided in 1935 by Weichselbaum[81]

Weichselbaum showed that rats, on a diet low in casein, after a few

attracted little attention at the time, but some four years later a series of papers began to appear on the experimental production of 'cirrhosis of the liver'.[12 13 14 15 16 23 41 42 43 58 59 69 74 79 80] In these attention was directed to the production of fibrotic lesions, but it was soon observed that, inconstantly and irregularly, rats on the diets devised to produce fibrosis showed lesions similar in appearance to the 'haemorrhages' described by Weichselbaum. The true nature of these was then recognized by György and Goldblatt[41] to be acute necrosis. All save

were simply a

. Daft, Sebrell

and Lillie,[24] however, on the basis of experiments showing that

different dietary supplements affected differently the incidence of necrosis and of fibrosis, suggested that the two conditions were [illegible]

[illegible]

included with dietetic necrosis and fibrosis and generally regarded as the initial and essential lesion in the sequence.

Research into the causation of dietetic hepatic injury was inevitably influenced by these views. If all dietetic lesions were regarded as but stages in a single sequence then it was reasonable to search for a single causative factor. If, on the other hand, this view was mistaken and there were actually several kinds of dietetic injury, then such a search would lead to confusion. This is apparently what happened. The most discordant results were received and it is no exaggeration to say that, at one time or another, different workers indicted every dietary component, save carbohydrate, as the causative agent so that Bollman,[14] writing in 1943, was driven to conclude that the lesion had numerous causes. In 1944, however, Himsworth and Glynn[36 49] brought forward evidence that there were two kinds of experimental dietetic injury, one, an acute massive necrosis, the survivors of which developed post-necrotic scarring and nodular hyperplasia; the other an insidiously developing diffuse hepatic fibrosis. A fibrosis of the liver ultimately develops from either injury, but the type differs in each and to only one is necrosis a necessary antecedent. The necrotic sequence is related to deficiency of protein and tocopherol, the diffuse hepatic fibrosis to fatty infiltration of the liver. This view has been justified by their producing one lesion independently of the other.

THE CLINICAL FEATURES OF THE TWO TYPES OF DIETETIC INJURY[49]

Massive Hepatic Necrosis and its sequelae

When rats are placed on an appropriate low protein diet they continue in apparently good health, and may even grow, for some weeks. Then illness develops. The more deficient the diet the shorter the latent period before the appearance of illness and the more severe and sudden its form when it appears. Animals active and well in the morning may be dead in the evening. First, they become quiet and huddle in the corner of the cage. Their temperature falls, they lose

consciousness, breathing is almost imperceptible, and then the animal quietly dies Rarely convulsions precede the end.

This clinical course is remarkable in several ways First, there is the long latent period, during the whole of which the animal, although exposed to the conditions necessary to produce illness, remains apparently healthy Second, there is the nature of the illness, which appears without any alteration in the environment, without any warning, and with a suddenness which is not usual in deficiency states.

u-

is

found. Subsequently amino-acids may appear in the urine, together with traces of urobilin and bilirubin, but clinical jaundice is rare in a first attack.

If the animal survives the acute illness the abnormal constituents disappear from the urine in a few days. Appetite returns in about a week and activity becomes normal. But, although the weight may again begin to increase, it rarely reaches the same level as that of unaffected animals of the same age. Subsequently one of three events may happen. The animal may continue in fair health. Another, and this time fatal attack, of massive necrosis may supervene. Jaundice, ascites, pericardial and pleural effusions, and oedema may gradually develop and the animal die with the signs of chronic hepatic failure and portal hypertension

Diffuse Hepatic Fibrosis

The clinical course of rats developing diffuse hepatic fibrosis is very different For several months after receiving a diet designed to produce fatty infiltration of the liver the animals grow steadily and show no signs of illness. Growth then ceases and the weight, after remaining *stationary for two or three months, begins to fall.* The fall is erratic, being interrupted by transient gains in weight. It continues for more months and then, usually, an intercurrent illness supervenes and at autopsy diffuse hepatic fibrosis is found. This sequence is in marked contrast to that of animals with dietetic necrosis 'The course is insidious, there are no episodes of acute illness The process is measured in months instead of weeks, and it is not until the weight has commenced to fall that even microscopic signs of liver fibrosis can be found with any certainty.



FIG 24—The stages of experimental massive hepatic necrosis produced by a low protein diet Rats × 1⅓

A Early acute stage 6–12 hours after the onset of symptoms
B Later acute stage Lesion 24–48 hours old
C. Subacute stage Lesion 3–14 days old
D Liver shrunken and distorted as a result of post-necrotic scarring and nodular hyperplasia Lesion probably 2 months old

(Glynn and Himsworth, *J Path and Bact*, 1944, 56, 297)

PATHOLOGICAL FEATURES OF DIETETIC LIVER INJURY

Massive Hepatic Necrosis and its sequelae[38]

The livers of animals killed, within an hour or so of appearing ill, are swollen, generally vermilion in colour but spotted on their surface

liver. Some twelve or twenty-four hours later the appearance has altered. The liver is, in general, pale yellow and spotted on its surface with bright red areas. It resembles the livers from human cases with 'acute yellow atrophy' (Fig. 24B). Two or three days to a week later the organ has the dull yellow appearance of Cheddar cheese but, on its surface, depressed dark-red areas of considerable extent (Fig. 24C) have now appeared. The appearance is that of 'subacute red atrophy'. In the course of some weeks the yellow gives place to normal liver colour, the red areas disappear and are replaced by depressed and irregular scars (Fig. 24D).

The sequence of microscopic changes show a similar close correspondence to those seen in human cases of massive hepatic necrosis In the earliest stage, found only in animals killed at the first sign of illness,

Within twenty-four or forty-eight hours of the onset of illness the classical picture of acute massive hepatic necrosis has developed In the affected areas every parenchymal cell is disintegrating but the Kupfer cells and the tissues of the portal tracts survive unscathed (Fig. 25). Later, at the stage of 'subacute red atrophy' the debris of dead cells has been removed. The sinusoids are dilated and engorged with blood

lobules gradually collapses, bringing neighbouring portal tracts into apposition Conspicuous proliferation of bile ducts occurs The site of necrosis thus comes to be occupied by an agglomeration of bile ducts, vessels and fibrous supporting tissues with, here and there, small groups of surviving parenchymal cells

The stage of post-necrotic scarring has now been reached, and as the

A

B

FIG 25—Massive hepatic necrosis. H and E × 118 A Rat. Low protein diet. The bile duc and blood vessels survive but all the parenchymal cells are dead. Infiltration with inflammatory ce is beginning B Man Causation undetermined Lesion at a slightly later stage than A Only few dead parenchymal cells remain Profuse infiltration with histiocytes and neutrophils.

condition is so commonly confused with other forms of hepatic fibrosis, it is necessary to describe its characteristic features in some

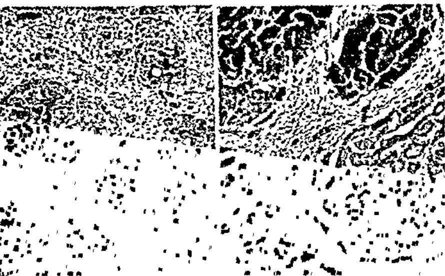


FIG 27—Massive hepatic necrosis Stage of [illegible]
H and E × 118
A Rat Low protein diet Nodules of parenchymal cells derived by continued [illegible] plasia from isolated groups of such cells surviving the original acute necrosis, are embedded in connective tissue in which are numerous proliferating bile ducts
B Man From a patient who survived 2½ years after a severe attack of jaundice while receiving neoarsphenamine

detail. Although macroscopic examination may suggest that the liver is uniformly affected in dietetic massive necrosis, microscopic examination shows that it never is Large areas of relatively healthy tissue survive between the areas of necrosis with the result that, when post-necrotic scarring occurs, the fibrosis is irregularly distributed through the organ (Fig. 5). At this stage bands of vascularized fibrous tissue, containing numerous proliferating bile ducts, cut sharply across or circumscribe, areas of liver composed of entirely normal lobules (Figs. 7, 34) Such areas of normal lobulation are the most characteristic feature of post-necrotic scarring They can be recognized with certainty by finding within them normal portal tracts standing in normal relationship to normal hepatic veins With the passage of time the compulsion to parenchymal hyperplasia, which occurs whenever

the amount of functioning hepatic tissue has been reduced, begins to manifest its influence. It affects not only the areas of normal liver lobules, but also, and more particularly, the isolated group of cells enmeshed in the scars. In the former larger but architecturally normal lobules are produced. But, because of the absence of a reticulin scaffolding, the isolated cells in the scars cannot produce liver lobules. The only course open to them is concentric hyperplasia and the result is nodules of parenchymal tissue devoid of lobular structure (Fig. 27). Concurrently with the parenchymal hyperplasia contraction of the scar tissue [illegible]

the par[illegible]

organ [illegible]

hyperplasia of the liver, or even hepar botryoides. In this type of hepatic fibrosis, therefore, there are two types of nodules; those which are merely masses of parenchymal cells and those containing normal liver lobules The former occur in other hepatic fibroses; the latter only in post-necrotic scarring. Careful search may be needed to find these, but once normal lobulation has been discovered in a fibrotic liver, it can be stated with confidence that the preceding lesion was a massive hepatic necrosis.

Diffuse Hepatic Fibrosis[49]

Diffuse hepatic fibrosis develops in livers which are the seat of heavy, prolonged infiltration and, in dietetic experiments, such infiltration is usually due to neutral fat. For the first few months while the animal is gaining weight, this is the only change found (Fig. 28A). Later, special stains reveal a thickening of the reticulin fibres in the region of the portal tracts or central veins. These fibres gradually extend to link up with each other so that, soon, there develops, throughout the whole liver a fine fibrous network isolating and intersecting

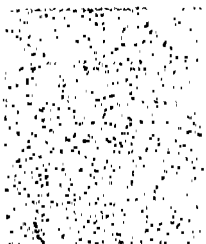
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take the stains for fibrous tissue (Fig 28C). Fat diminishes in the organ so that its colour changes from bright yellow to buff or bronze The fibrous tissue contracts and the circumscribed parenchyma proli-

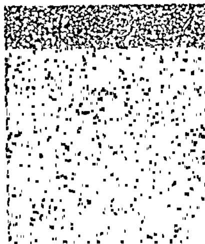
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portal tract or central vein, and it is no longer possible to distinguish the original portal tracts, even by injecting the biliary system with Indian

A

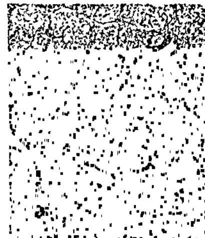


B





C



D

FIG 28—Diffuse hepatic fibrosis (51) Experimental Rat High fat, moderate protein diet Laidlaw s reticulin stain × 44 Compare with Fig 39

A Fatty liver

ink, for bile ducts have grown along the fibrous bands so that, not only portal veins and hepatic arteries, but central veins also have now



FIG 29—Diffuse hepatic fibrosis. Experimental Rats (51) High fat, moderate protein diet ¾ natural size From left to right —
Early stage The liver is enlarged and covered uniformly with fine granulations
Intermediate stage The liver is covered with fine granulations, some of which are under-

gan is
No

their accompanying bile ducts Ensnared portions of lobules have hypertrophied concentrically to form nodules devoid of the normal vascular pattern, and eccentric atrophy of other lobules has occurred so that any remaining veins are taken up in the surrounding fibrous tissue The parenchymal cells themselves show less fat but minor degenerative changes (Fig 28D). The classical picture of 'portal cirrhosis', or as it can more precisely be termed, diffuse hepatic fibrosis, has insidiously developed. The sequence of gross changes is shown in Fig 29.

In distinguishing this condition from post-necrotic scarring there are three features that must be stressed. First, the development is insidious, not sudden. Second, frank necrosis does not occur at any stage. Third, the process is uniform and when the lesion is established, every lobule is affected and no normal lobulation can be found.

THE CHEMICAL PATHOLOGY OF DIETETIC INJURY

Massive Hepatic Necrosis

Livers showing the acute necrosis are enlarged and, compared with livers from unaffected animals on the same diet, are heavier in propor-

tion to the body weight (Fig. 30).[37] They contain no glycogen, a decreased proportion of protein, and an increased proportion of water. In early lesions the amount of non-protein nitrogen is normal, but in animals which have lingered for some days it may be increased, presumably as a result of autolysis of the necrotic tissue. Necrotic livers contain no more fat than normal livers from animals taking the same diet, and no correlation between necrosis and fatty infiltration can be demonstrated (Fig 31). Particular importance attaches to this observation because fatty infiltration has been regarded as a necessary precursor of dietetic necrosis.[43] The increase in size and weight of affected livers is due to oedema Such oedema is confined to the liver It can be accounted for by infiltration of the organ with a fluid containing protein in the concentration of approximately 9 g /100 c c As a result of such infiltrations the protein content of the liver as a whole is increased but, the protein concentration in the oedema fluid being less than that in normal liver tissue, the concentration of protein in the affected organ is reduced The water of the oedema fluid is apparently derived from the plasma, for, simultaneously, haemoconcentration occurs. The source of its protein is obscure It cannot be cellular infiltration, as an increase of total protein in the liver is found before this occurs. It may be the plasma proteins, these being concentrated by precipitation in the oedematous organ Lymphoedema from compression of the intrahepatic lymphatics by the swollen parenchymal cells may also contribute. These changes in composition are not characteristic of necrosis

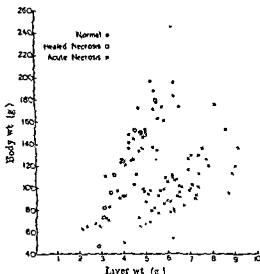


Fig 30—Relation of the weight of normal rats' livers, and of livers from rats with dietetic massive necrosis, to body weight (Himsworth and Glynn, *Biochem J*, 1945, 39, 267)

for they occur, but to a less extent, in minor degenerations such as cloudy swelling.[37 53 65 78] They do, however, occur suddenly. If, when

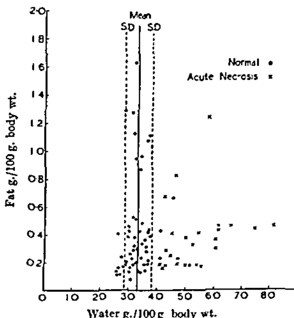


Fig 31—Dietetic, massive, hepatic necrosis Correlation between necrosis and increase of liver water and absence of correlation between necrosis and liver fat content S D—standard deviation of the series (Himsworth and Glynn, *Biochem J*, 1945, 39, 267)

necrosis affects a few of the animals in a herd on the necrogenic diet, the whole herd is killed, the livers are found to be either entirely normal or abnormal in composition Transitional changes of composition are not found But the abnormal chemical findings do not persist. The livers of survivors are of normal composition and, although conspicuously distorted in shape, are chemically indistinguishable from those of unaffected animals

Diffuse Hepatic Fibrosis [51a]

When animals are given a diet which produces heavy fatty infiltration of the liver the concentration of fat in that organ rises rapidly to a maximum in the first few weeks and, thereafter, falls gradually so that when diffuse hepatic fibrosis is fully developed the fat content may be within normal limits. [37a] Livers which are the seat of diffuse fibrosis contain more water and protein, in proportion to the body weight, than normal livers. But these changes are not characteristic of

fibrosis for they occur, although to a lesser degree, with fatty infiltration long before there is any sign of fibrosis. No excess of water and protein is found until the concentration of fat has risen above 15% of the wet weight of the liver. At higher concentrations the excess is roughly proportional to the fat content As fibrosis develops, however, the excess continues to increase despite the fall in the fat concentration From the standpoint of gross chemical composition, therefore, livers in the pathological sequence from fatty infiltration to diffuse hepatic fibrosis constitute one smooth sequence of qualitatively similar, but quantitatively increasing, change, and it is evident that the essential changes in composition of the organ have been initiated long before there is any pathological evidence of damage. Evidence has already been presented that in livers grossly distended with fat the blood sinusoids are compressed It seems reasonable to suggest that under similar conditions the lymphatics are similarly compressed, thus leading to a retention of lymph in the organ which would account for the observed excess of water and protein. In many pathological processes chronic lymphoedema forms a basis for the development of fibrosis.

THE PATHOGENESIS OF DIETETIC MASSIVE HEPATIC NECROSIS

The Dietary Factors Responsible

[illegible]

it is not due to excess of fat which, indeed, tends rather to mitigate than to facilitate its development The dietary correlation is with cystine and tocopherol

The role of cystine was elucidated on rats receiving a diet unsupplemented with tocopherol The development of the lesion was, under these circumstances, found to be correlated with the intake of protein; not the proportion in the diet, but the absolute amount eaten each day.[49] When casein is the source of protein, an albino rat of a pure Wistar strain requires at least 500 mg. daily to prevent the lesion With 200 mg. daily, generalized necrosis soon develops, with intermediate values it appears

[illegible]

develop rapidly, and amounts as large as 1500 mg. daily are insufficient to prevent its occurrence.[49] The most obvious difference between yeast protein and casein is that the former is poor in methionine; and it was found that when the yeast diets were supplemented with 20 to 21 mg. of methionine daily, necrosis was prevented.[50] Previously Daft[21] [illegible]

[illegible] experiments with the same object had reported that methionine retarded the development of 'cirrhosis'. Unbeknown to either the American or English workers, Hock and Fink[52] in Germany were working on similar lines. They also used yeast as their source of protein, correlated the development of necrosis with the poverty of their [illegible]

[illegible] the lesion. This *problem presented particular difficulties* because, methionine being converted to cystine in the body,[70 82 83] and cystine [illegible] of methionine[84] administration of [illegible] conserves whatever supplies of methionine are available to the animal. *By a fortunate observation, however, the solution was found.* Using diets in which the sole source of nitrogen was supplied by a mixture of synthetic amino-acids, it was observed that methionine deficiency, *when ample cystine was present,* led *to the development of a macro*-cytic anaemia and hypoproteinaemia but not to necrosis. These lesions were preventable by even small amounts of methionine. But if cystine *were omitted from the diet, yet just sufficient methionine* given to prevent ana[illegible] massive necrosis developed [illegible] of *dietetic* mas[illegible] deficiency of cystine[38]

The relationship between dietary massive necrosis and tocopherol *deficiency* emerged later. In 1944 Schwarz[70a] produced necrosis of this type, in rats, by means of a diet containing as much as 15% of an alkali-treated casein, but observed no lesion when crude casein was used in the same amounts. The lesion developing on the special casein diet was prevented by supplements of wheat germ and the preventive factor was later shown to be tocopherol.[70b] At the time these results were not generally available, but György[70d] independently produced

similar evidence. Searching for the explanation of the inconstancy with which massive necrosis occurred in animals on his diets, he noted a relationship between the incidence of the lesion and the type of fat in the diet; and later correlated this with the tocopherol content of the fat. He then showed that the incidence of the lesion on a diet deficient in sulphur-containing amino-acids was decreased by supplements of tocopherol, although adequate dietary cystine prevented the lesion

to rats taking their most effective necrogenic diet—that supplying 500 mg. of yeast protein daily—prevented the development of massive hepatic necrosis Next, inquiry among the English workers who had been unable to produce the lesion, elicited the information that they had added supplements of tocopherol to the yeast protein diet under the impression that instructions to use such had been inadvertently omitted from the published account. On repeating their experiments without adding tocopherol typical lesions were obtained. But this did not entirely remove the discrepancies between the results from different laboratories. While Himsworth and Lindan still continued to obtain a 100% mortality among their animals when using the yeast diet, few other workers obtained more than a 30% mortality and some still reported no lesions at all Knowing that the muscular lesions of tocopherol deficiency only appeared after long periods of deprivation, it seemed possible that, if the pre-experimental diet were rich in this vitamin, sufficient supplies might be carried over into the experimental

tocopherol twice weekly. After one hundred and seven days on these diets the animals were given the yeast protein diet without tocopherol The rats which had previously received the tocopherol supplement died in an average of one hundred and twenty days (S E. ±3·8), those that had received no such supplements in sixty-five days (S E. ±8·8) It is known that relatively little tocopherol is provided by the maternal milk and that rats do not acquire this vitamin in quantity until they begin to take ordinary food, some ten days after birth. To test the matter further rats and their litters were given the tocopherol-free diet on the tenth day after birth and the yeast-protein diet on weaning at the twenty-third day. Deaths from massive necrosis occurred with remarkable rapidity, appearing on the tenth day and most of the

animals being dead by the thirtieth. It is thus clear that the state of the tocopherol reserves at the beginning of the experiment is of great importance. But, whatever the degree of tocopherol depletion before the low-cystine diet is given, adequate supplements of either tocopherol or cystine will completely protect against the development of massive hepatic necrosis as long as—and for some time after—either is given.

These findings go far to explain the discrepancies between the results from different laboratories. But there are other factors. As in all dietary experiments the age of the animal is of importance, the young and growing animal being much more susceptible. Thus, if the cystine deficient diet is given immediately on weaning to rats which have had access only to a tocopherol-free diet since the tenth day after birth, the majority will be dead of necrosis before the thirtieth day; if it is withheld until the one hundred and thirtieth day after birth the average time of death will be sixty-five days. Sex also probably plays a part, male rats appearing more susceptible than females. Again, there are considerable variations in the time taken by different strains of rats to develop the lesion. On the yeast protein diet, rats from the Glaxo herd of pure Wistar strain usually develop a severe lesion in about fifty days, rats from an impure albino strain in approximately one hundred days, while black-hooded rats may survive unharmed, or show only mild and partial lesions, after two hundred days. These differences may have a genetical basis but the possibility that they may depend on factors acquired from early environment, such as differences in intestinal flora, has not been disproved. And there is always the possibility of unsuspected differences between the ostensibly similar foods used in different laboratories. Professor Paul György informs me that, although he has no difficulty in producing massive necrosis using the English yeast which I used, he is unable to produce the lesion with his strain of American yeast. Both yeasts are free from tocopherol and the differences in the amount of sulphur-containing amino-acids between them seem altogether too small to account for this contrast in results so that some such possibility as differences in the ease of liberation of their amino-acids on digestion seems to be indicated.†

But given animals of the same strain and age, and food of identical composition, it is now clear that massive hepatic necrosis can readily be produced in rats by a diet deficient in cystine and tocopherol; and, further, that this lesion can be prevented by supplementing such a diet with either cystine or tocopherol.

The Production of Dietetic Massive Necrosis

The fact that massive hepatic necrosis develops in animals receiving a diet deficient in cystine and tocopherol does not in itself prove that the lesion is directly attributable to dietary deficiency The influence of diet on the susceptibility of experimental animals to various poisons has long been recognized and, as will be shown later, there is good clinical evidence that malnutrition increases the liability of human subjects to severe liver injury in infections which cause hepatitis. It was, therefore, natural to search for a hidden adjuvant to the action of the nutritional deficiencies

The nature of the experiments excludes the possibility of exposure to an extraneous chemical poison Repeated cultures from livers showing massive necrosis have failed to reveal any bacterial infection and 'passage' experiments, in which a brei of affected livers was used for the first injection, have produced no evidence of infection by viruses [60] Further, groups of rats from different litters and housed in different institutions develop the lesion at approximately the same time after receiving the appropriate diet, and

agent is conceived it must be one which is normally harboured by many animals but which only produces pathogenic effects when cystine and tocopherol are deficient

There is, however, another possibility, a toxic factor might be produced actually within the body, it being envisaged that changes occur in the intestinal flora and that the new flora elaborate the toxic agent Certain observations on massive necrosis might be interpreted on this basis Occasionally animals are observed which survive unharmed for long periods after all their fellows on the same diet have died It is difficult to conceive of such prolonged survival under conditions of dietary deficiency as the result of a failure to deplete the animal of nutriments. Mention has already been made of the predilection of dietetic

possibility that, for various reasons, the different proteins do not all yield up their constituent amino-acids with the same facility during digestion, is one which requires close attention in relation to dietetic necrosis

animals being dead by the thirtieth. It is thus clear that the state of the tocopherol reserves at the beginning of the experiment is of great importance. But, whatever the degree of tocopherol depletion before the low-cystine diet is given, adequate supplements of either tocopherol or cystine will completely protect against the development of massive hepatic necrosis as long as—and for some time after—either is given

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and the differences in the amount of sulphur-containing amino-acids between them seem altogether too small to account for this contrast in results so that some such possibility as differences in the ease of liberation of their amino-acids on digestion seems to be indicated †

tics of massive necrosis. How cystine deficiency produces such swelling is, as yet, uncertain. No significant premonitory changes have been detected in the environment of the parenchymal cells, and on general grounds it would seem probable that the disturbance originated within the cell. But whatever the explanation of the mechanism of this swelling it must account for two observations. First, that it only develops after the animal has been for weeks on the deficient diet, and second that, when it does develop, it appears suddenly. The inference is that the essential disturbance causing swelling of the liver parenchyma only occurs when the degree of deficiency has fallen below a certain minimum, that weeks of depletion are required to reach this level, and that until it has been passed the liver cells function normally

Sulphur Metabolism and Hepatic Necrosis[47a]

From the whole subject of hepatic necroses an association with derangements of sulphur metabolism is beginning to emerge and, although the relationships between many observations are still largely conjectural, it may be profitable to consider the matter as a whole at this stage This will necessarily involve considering data which will be treated more fully in subsequent chapters

Necrosis of the liver can be produced by deficiency of cystine, by chlorinated hydrocarbons, by poisons such as selenium, by deficiency of tocopherol, and also by administration of excessive amounts of cystine In all save the last the lesion is aggravated by deficiency, and mitigated by sufficiency, of the sulphur-containing amino-acids Cystine deficiency leads to a profound fall in the glutathione concentration in the liver, which is speedily remedied by giving this amino-acid.[65] Selenium replaces sulphur in the amino-acids of grain grown on seleniferous soil and, as its toxic effects can be prevented by sulphur-containing amino-acids, it presumably acts by producing a conditioned deficiency of cystine in the bodies of animals subsisting on such grain[63b] Chlorinated hydrocarbons deplete the liver of glutathione[11a] and readily inactivate the sulfhydryl groups of certain enzymes.[62a 66a] Susceptibility to the chlorinated hydrocarbons is increased by deficiency [illegible]

[illegible]

the observed association between cystine and tocopherol deficiency In their brilliant article on the role of tocopherol in metabolism, Hickman and Harris[46a] have concluded that this strong reducing agent is probably concerned in preserving the requisite intracellular concentra-

massive necrosis for the left lobes of the liver, which receive portal blood from the colon and spleen, in contrast to the right lobes, whose portal blood comes from the small intestine. This predilection has been attributed to the left lobes, under conditions of dietary deficiency, becoming depleted earlier than the right by reason of the blood reaching them being poorer in the protective nutriments liberated from the food during digestion in the small intestine But there is an alternative possibility. The flora in the colon might, under appropriate dietary conditions, be such as to produce a toxin capable of causing hepatic necrosis and which, being carried to the left lobes of the liver, would produce a lesion in that site. Experiments in which large doses of succinyl-sulphathiazole were given to rats failed, however, to produce any evidence in favour of this idea and, incidentally, for a related idea that different intestinal flora might influence the supply of protective

by

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with any hypothesis which postulates the existence of a toxin. Areas of massive necrosis in the liver are often accurately confined to sites of pressure by neighbouring structures such as the costal margin or stomach Pressure presumably acts by retarding blood flow, and such retardation, while favouring depletion of blood-borne factors, would tend to protect against blood-borne toxins. It has already been noted that in fatal human cases of acute massive hepatitis, whether these be due to poisons like trinitrotoluene and cinchophen or to infections like virus hepatitis, the left lobes of the liver are frequently more heavily damaged than the right It is difficult to believe that this phenomenon, which follows on such diverse causes, is dependent upon the coincidental elaboration of an adjuvant necrogenic agent in the colon.

The present position is, therefore, that, although deficiency of cystine and tocopherol have been established as essential to the production of experimental, dietetic, massive necrosis, no evidence has been obtained that any positive factor, infective or toxic, is necessarily involved.

The original reluctance to accept a florid lesion like dietetic massive necrosis as the result of a nutritional deficiency has now been largely removed by appreciating the part played by circulatory factors in its production. It is only necessary to postulate that the deficiency leads eventually to severe swelling of the hepatic parenchyma for, once such is produced, the peculiar circulatory arrangements in the liver will automatically ensure the development of a lesion with the characteris-

that lipotropic properties were not confined to choline. Casein,[8,19] egg white and beef muscle,[5] were also found to be effective. In the search for the active component in protein the effect of many individual amino-acids was studied but none were found to be lipotropic[2,3,4] save methionine[11,18,77] The relationship between the lipotropic actions of choline and of methionine was then demonstrated by du Vigneaud in a remarkable series of investigations,[26,27,28] which showed that the methyl group of methionine may be used for the synthesis of choline. These considerations explain why diffuse hepatic fibrosis is prevented when adequate supplements of choline are added to a high fat diet and why it develops in animals subsisting on a low fat, but choline poor, diet[59] They also show how high protein diets may prevent the lesion[44,51]

But there are also substances which seem actually to promote fatty infiltration of the liver. Of these cystine is the best known and to explain its action two suggestions have been made. The first postulates an antagonization of the lipotropic action of methionine by cystine and, according to it, the degree of fatty infiltration depends, not upon the absolute amounts of either amino-acid present, but upon the ratio between them.[76] The second ascribes the alipotropic action of cystine to its power of promoting growth when the supply of dietary methionine is suboptimal and envisages that in such growing animals methionine is diverted to the formation of tissue protein and so is not available to act as a lipotropic agent.[64] Be this as it may, several workers[24,43,80] have observed that cystine accelerates the development and exaggerates the lesions of experimental 'dietetic cirrhosis'.

Certain vitamins influence fatty infiltration. Thiamine is necessary for the development of the fatty liver due to choline deficiency.[61,62] Biotin causes a considerable deposition of liver fat, which is said by some workers to be unusually rich in cholesterol, and to be prevented by inositol but not by choline[32,33,34] Other workers,[10] while confirming the lipotropic action of inositol, were unable to demonstrate any excess of cholesterol or a resistance of this type of fatty infiltration to choline. Riboflavin deficiency is said to lead to gross fatty infiltration[71,72,73] and pyridoxine is reported to exert a lipotropic action.[40] The mechanism of action of these factors has not as yet been deeply investigated nor their influence upon the development of diffuse hepatic fibrosis determined In view, however, of the evidence that supplements of tocopherol reduce the liability of rats to develop the massive hepatic necrosis due to cystine deficiency[40a] it is worthy of

tion of the reduced form of certain enzymes It is conceivable that tocopherol may be concerned in maintaining the equilibrium between reduced —SH and oxidized S-S glutathione at a point in favour of the former. If this were so, a deficiency of tocopherol would lead to a reduction in sulfhydryl groups as effectively as an actual deficiency of cystine. There remains the paradox of cystine poisoning[22], but, if the oxidized and reduced forms of glutathione constitute an oxidation-reduction potential system of the type envisaged above, addition of a gross excess of the S-S form, in the shape of cystine, would be expected to upset the balance and impair the efficiency of the whole system. Thus it is possible to account for the common result of these diverse measures by a single, if highly speculative, hypothesis—that reduction of the active sulfhydryl groups within the cells, however, produced causes changes which lead to necrosis.

THE PATHOGENESIS OF DIETETIC DIFFUSE HEPATIC FIBROSIS

The Dietary Factors Responsible

Heavy, prolonged fatty infiltration of the liver, irrespective of its cause, is the invariable antecedent in the production of nutritional diffuse hepatic fibrosis. The heavier the infiltration the more rapid the development of the fibrosis. Thus, in rats in which the attained percentage of liver fat is persistently of the order of 30%, the first indications of the lesion may be found within a hundred days of commencing the diet; if it is of the order of 15% similar indications may not appear for over three hundred days, if at lower levels no lesion develops [37a]

The conditions governing fatty infiltration of the liver have been the subject of intensive study during the last decade, and it is now established that such infiltration can be produced, not only by diets rich in fats, but by diets deficient in factors which normally prevent the accumulation of fat in the liver. These preventive substances have been termed 'lipotropic factors' and their existence was first demonstrated in relation to fatty infiltration in the livers of depancreatized dogs Lecithin was found to be effective in such prevention.[45,46] and [illegible] was soon shown to be choline[47] This

[illegible]

liver to normal, and that, in the absence of choline, fatty infiltration occurs even though the diet is devoid of fat. It was soon appreciated

of the intra-lobular circulation has already been directly demonstrated (Fig. 23). It is believed that, as a result of this impediment, the slowly circulating blood is largely depleted of its nutriments by the time it has progressed some distance down the sinusoids. As a result the more central cells are malnourished and ultimately degenerate and disappear. The situation is analogous, though of a lesser degree, to that in repeated attacks of centrilobular necrosis; and in both cases a diffuse hepatic fibrosis results. Whether the accumulation of fat within the cell interferes with vital cellular activity, and so predisposes to degeneration, is uncertain. That it interferes with mitosis and so retards the replacement of degenerated liver cells is suggested by recent work.[68b]

MIXED LESIONS

Evidence has now been presented that, by means of carefully selected experimental diets, two distinct forms of dietetic injury to the liver can be differentiated. It so happens, however, that the nutritive factors, whose deficiency leads to one or other lesion, tend to occur together in nature. Thus, meat supplies not only sulphur-containing amino-acids but also lipotropic factors such as choline. Further, a factor which is essential for the prevention of one lesion may incidentally possess a general property which contributes to the prevention of the others. Methionine acts both as a source of [illegible]

consideration is of importance for the interpretation of much of the available experimental work. It is, perhaps, of even more importance for the understanding of certain hepatic lesions occurring in man.

Applying the criteria laid down for the recognition of diffuse hepatic fibrosis to data in the published reports on 'dietetic portal cirrhosis', it will be found that only in relatively few instances is there unequivocal evidence that an uncomplicated diffuse fibrosis has been produced. Rich and Hamilton[69] have produced it in rabbits, Spellberg and Keaton[74] in guinea-pigs, Blumberg and Grady,[12] Lillie, Daft and Sebrell[59] and Himsworth and Glynn[49] in rats, and Chaikoff and his colleagues[16] in dogs. All these writers are agreed as to its pathology [illegible]

less clear. In some, insufficient data are given for the recognition of the

note that tocopherol does not prevent the development of the diffuse hepatic fibrosis consequent upon fatty infiltration [51]

Lastly, diffuse hepatic fibrosis has been observed after hypophysectomy. It is always associated with a fatty infiltration referable, perhaps, to changes in the animal's habits of feeding [38a]

Consideration of the fatty infiltration which precedes diffuse hepatic fibrosis, cannot be left without reference to the substance 'ceroid', which has been found in the livers of rats with this lesion.[12 40 41 58 59] This substance stains with Sudan IV, *fluorescences*, but is not soluble in fat solvents. It occurs as globules in the fibrous tissue bands. It is commonly seen in the 'dietetic cirrhosis' of rats. Ceroid is not found in the similar fibrosis of dogs,[16] but opinion is divided as to whether it is present in the morphologically identical human fibrosis [67 68] It is absent from the diffuse fibroses due to carbon tetrachloride poisoning,[40] and in the post-necrotic scarring following selenium poisoning,[58] Occurring frequently, and being first recognized, in the livers of rats showing 'dietetic cirrhosis', it was not unnatural to think that it might be of aetiological significance. Further investigation showed, however, that ceroid could be formed from unsaturated fatty acids by other tissues,[31] and indications of an association with deficiency of vitamin E have been obtained [67] It seems, therefore, that ceroid is to be regarded as an incidental result of the diets used rather than as an essential factor in the production of hepatic injury.

The Production of Diffuse Hepatic Fibrosis

It has been mentioned previously that the intralobular circulation is impeded when the parenchymal cells are swollen with fat. This mechanical interference occurs irrespective of the nature of the infiltrating agent. When macromolecular substances, such as silica gels [39] or polyvinyl alcohols,[54] are injected repeatedly into the circulation, they are removed by the Kupfer cells and hepatic parenchyma, and these soon become grossly distended *Diffuse hepatic fibrosis,[39] and in* some cases centrilobular necrosis [54] result. Diets rich in cholesterol produce a similar infiltration of the liver and lead to a similar diffuse hepatic fibrosis,[17 47 56] even more readily than diets containing only glycerol esters of fatty acids [80] (Fig. 50). These considerations point to a mechanical factor in the production of such liver lesions and, indeed, [illegible] by Connor [20 21]

[illegible]

by parenchymal cells infiltrated with fat and the consequent impeding

abnormal diet is due to these receiving most of the dietary lipotropic factors which, if the diet is not too rich in fat, are sufficient to prevent fatty infiltration. Because these diets are not grossly abnormal, animals receiving them survive a considerable time. Hyperplasia has thus time to occur, and frequently, in animals surviving for one or two years, [illegible]

and are not, as was thought originally, diagnostic of post-necrotic scarring.[48] The distinction between them must be made on the nature of the fibrosis in each case. It can, therefore, be said that grossly abnormal diets produce generalized hepatic lesions, while partly abnormal diets produce lesions confined to the left lobes of the liver.

'Subacute' (Recurrent Limited) Massive Necrosis[176]

Partial lesions in the livers of rats which have survived for a considerable period will be found to show, at one and the same time, every stage in the massive necrosis sequence from acute necrosis to post-necrotic scarring. Speaking clinically their illness can be said to run a subacute course But if animals are killed at various stages in this course it will be found that the condition is one, not of subacute necrosis, but of successive, limited attacks of acute massive necrosis. In the earliest stage the condition differs from a fatal attack of massive necrosis only in being limited to a small area of several liver lobules. Bordering this area is a band in which the necrosis is irregularly zonal and beyond this the liver is entirely normal (Fig. 32). The area of massive necrosis develops into a scar. The lobules affected by the zonal lesion are reconstituted but show some residual fibrosis in the portal tracts Further attacks occur and areas of post-necrotic scarring link up to isolate multi-lobular nodules (Fig 32c). Then massive necrosis hits these nodules themselves And so the process smoulders along, the animal never being acutely ill but never in good health. The importance of this lesion lies in its being similar to the pathological process in human cases of subacute hepatitis, its interest in its possible explanation Throughout the whole course the animal is exposed with the same intensity to the factors causing necrosis, yet the necrotic attacks are intermittent. It is suggested that the explanation lies in local differences in circulation. The early attacks occur in areas of parenchyma which are normally less freely supplied with blood, and therefore suffer depletion earlier, than the rest (p. 39) Contraction of

lesion produced, little more being said that that 'dietetic cirrhosis' has been produced. In others it is evident from the illustrations that mixed lesions have been produced and these range from almost pure examples of massive necrosis, or post-necrotic scarring, through a variety of mixed lesions to almost uncomplicated examples of diffuse hepatic fibrosis. Such a variety is particularly apt to be produced by diets poor in protein and rich in fat; and it is not difficult to see why such have been extensively used. It was early appreciated that fatty infiltration contributed in some way to the development of fibrotic lesions in the liver The lipotropic action of protein was by then well established. It was only natural to test the effect of low-protein high-fat diets, and the conspicuous lesions produced rapidly established the reputation of such Equally naturally these results led to the unitary conception of dietetic injury of the liver and confusion with regard to its pathogenesis and to the effects of such substances as cystine and choline in its prevention

PARTIAL LESIONS

In discussing the influence of circulatory factors on the localization of liver lesions, reference was made to the partial type of massive necrosis which is confined to the left lobes of the liver Within the area affected such partial lesions are no whit less severe than, and pass through the same sequence as, the generalized form A similar, but less marked, predilection for the left lobes is occasionally seen in diffuse hepatic fibrosis Partial lesions of either kind occur particularly in animals taking diets which are only partly abnormal; in the case of massive necrosis, diets which are only partly deficient in protein and, in the case of diffuse hepatic fibrosis, diets which cause only moderate fatty infiltration of the liver. The reason suggested for the survival of [illegible]

begins, and continues to be most pronounced, in those lobes. *If small* doses of choline are given to animals on high fat diets, whose livers are generally infiltrated with fat, the earlier and more complete clearing of the right lobes can be readily observed. Presumably, therefore, the relative freedom from fat of the right lobes in an animal on a partly



FIG 32 C

FIG 32—Subacute (recurrent limited), acute, massive hepatitis Rats Low protein diet

A First attack of massive necrosis Massive lesion to the right, irregular zonal lesion to the left X 25 Haematoxylin and eosin
B Second attack of massive necrosis Cellular scar, with proliferating bile ducts to the left, massive necrosis in previously healthy parenchyma to the right X 45 Haematoxylin and eosin
C Post-necrotic scarring after limited attacks of massive necrosis On either side scars at the

the resulting scar tissues gradually restricts the blood supply to other localized areas of parenchyma Nutritional depletion and necrosis follow, and so the process continues

THE EFFECT OF GROWTH IN PRECIPITATING NUTRITIONAL INJURY

It is a commonplace that the state of nutrition influences growth; it is less readily recognized that growth can lead to malnutrition In the case of experimental dietetic injury to the liver this may be of



Fig 32 A

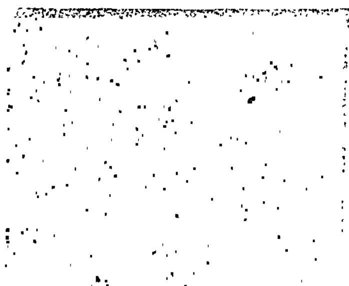


Fig. 32 B

deficiency consequent upon the derangement of the intralobular circulation produced by fatty infiltration of the parenchyma

Massive hepatic necrosis can definitely be shown to develop independently of fatty infiltration. Diffuse hepatic fibrosis cannot be directly shown to be independent of protein deficiency, for administration of an excess of protein prevents the necessary accumulation of fat in the liver But diffuse hepatic fibrosis can be shown to develop when the protein intake is sufficient to prevent the occurrence of massive hepatic necrosis. Rats were placed on a series of equicaloric diets containing constant amounts of casein, cystine and tocopherol but varying proportions of fat and carbohydrate. The amounts of casein, of cystine and of tocopherol were each sufficient to prevent necrosis. Diffuse

inadequacy of protein was responsible for this fibrosis was shown by adding choline to these diets when, the fatty infiltration being prevented, diffuse hepatic fibrosis did not develop But it is quite possible that the supply of protein might be relatively inadequate if the liver is grossly infiltrated with fat, for under such circumstances the slowly percolating blood in its course through the intralobular sinusoids may be more completely depleted of nutriments than blood of the same composition freely flowing in a normal liver and, in consequence, the centrilobular cells be brought into a state of protein depletion Two experiments by Handler and Dubin[41] lend support to such a suggestion They showed that fatty infiltration led to hepatic fibrosis, and in some cases even to centrilobular necrosis, when the diet contained only 5% of casein, but that, if it contained 18%, the lesions were minimal

The situation is, therefore, that, in the presence of fatty infiltration, diffuse hepatic fibrosis can develop when the protein intake is sufficient entirely to prevent dietetic necrosis With higher protein diets the lesion does not develop, but it is uncertain if this is due to such diets reducing fatty infiltration or to their producing an abundance of nourishment for the parenchyma cell. It is possible that both these effects occur But whether the local malnutrition within the infiltrated liver be due to lack of

deficiency, or simply

fact remains that the

of the liver, known as diffuse hepatic fibrosis, does not develop in the

such a degree as to produce severe lesions or death. This is well illustrated by the following experiment.

Three groups of rats were given the same fat free carbohydrate diet in equicaloric amounts which supplied 500 mg. of casein daily to each animal. A daily supplement of 50 mg. of cystine was given to the rats of the second and third groups and those in the latter also received 5 mg. of choline daily. Both groups receiving cystine grew more rapidly than the control group although all consumed the same amount of food. The livers of the control group contained slightly more fat than normal; those of the group receiving choline and cystine had a normal fat content throughout, those of the group given cystine alone developed gross fatty infiltration, while they were growing, and towards the end of this period an early diffuse hepatic fibrosis deve[illegible]
of cy[illegible]
and [illegible]
found. Apparently the acceleration of growth, consequent upon supplying adequate amounts of cystine, had outrun the supply of lipotropic factors in the diet and fatty infiltration had resulted to such a degree as to lead to hepatic injury.

THE POSSIBLE RELATION BETWEEN MASSIVE NECROSIS AND DIFFUSE HEPATIC FIBROSIS PRODUCED BY DIET

The statement can now be made that dietetic massive necrosis of the liver is attributable to a specific nutritional deficiency. A similar statement cannot be made regarding diffuse hepatic fibrosis. Nevertheless, the possibility that the two are related must be considered Reference has already been made to the effect of parenchymal infiltration in impeding the intralobular circulation and to the possibility that this may lead to degeneration in the lobule. Repeated zonal necrosis within the lobule is known to lead to a diffuse hepatic fibrosis. The distinction between zonal necrosis and massive necrosis due to poisons is simply one of degree. It might well be asked, therefore, whether the essential injury in diffuse hepatic fibrosis is fundamentally different from that in massive hepatic necrosis Might not both be due to protein deficiency? Massive necrosis would then be the expression of a severe deficiency, diffuse hepatic fibrosis the expression of repeated, but quieter, zonular damage due to a milder local protein

[40a] GYORGY, P '6th Conference on Liver Injury' Josiah Macy Jr Foundation Conference, May, 1947, p 67

Pub Health Report, 1942, 57, 502.

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absence of fatty infiltration. Fatty infiltration of the liver is, therefore, its approximate cause.

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cirrhosis', and recognized that it was the sequel to extensive necrosis. This type of hepatic fibrosis has long been recognized as particularly

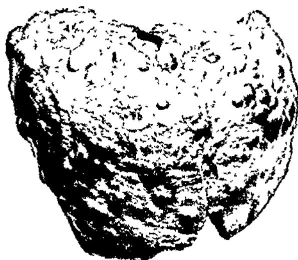


FIG 33—Post-necrotic scarring The liver is atrophic, contains much fibrous tissue and is irregularly studded with large nodules Specimen from the female case described on p 175

prone to affect the left lobes more than the right,[18 19 65] and to show coarse, irregular nodulation, rather than a uniform, fine granularity (Figs 33, 34)

Despite Mallory's clear description of this lesion, however, pathologists in general have shown a reluctance to accept it as a distinct entity In part this seems to be due to inappropriate terminology, in part to the difficulty of distinguishing with certainty many examples from other forms of hepatic fibrosis The terminology is inappropriate in two respects First, as pointed out by Karsner,[35] there is no evidence that a toxin is concerned in the production of the majority of cases. Second, the condition does not satisfy Moon's criteria for distinguishing 'cirrhosis of the liver'[45] He required that the lesion show evidence of

CHAPTER IV

NUTRITIONAL FACTORS IN LIVER INJURY: HUMAN

It is now possible to examine diseases of the liver in man in order to see if any are comparable to those produced by experimental dietary deficiency in animals. Such an examination can best be approached by applying the criteria, which distinguish the different forms of experimental nutritional injury, to pathological material from human cases of liver disease. If, thereby, similarities are disclosed, the clinical and aetiological features of the particular human disease can then be analysed for evidence that nutritional factors are concerned in its production

PATHOLOGICAL CONDITIONS IN MAN RESEMBLING THE LESIONS OF EXPERIMENTAL DIETETIC INJURY

Massive Hepatic Necrosis

The resemblance between the acute lesions, and immediate sequelae, of dietetic, massive hepatic necrosis in animals and the conditions in man first distinguished by Rokitansky,[53] and termed acute yellow and subacute red atrophy of liver, is so close as to require little comment Macroscopically the lesions in animals are but miniature reproductions of those in man (Fig 24); microscopically they are indistinguishable[26] (Figs. 25, 26, 27).

Post-necrotic Scarring of the Liver

It will be remembered that the distinguishing feature of this condition in experimental animals is the presence of a coarse fibrosis which separates and circumscribes areas of liver in which normal lobulation is preserved (Fig. 7). Less important, although conspicuous, is the parenchymal hyperplasia which affects both the areas with normal [illegible] tissue,
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careful search that areas with normal hepatic lobules can be found. These are recognized with certainty by the presence of essentially normal

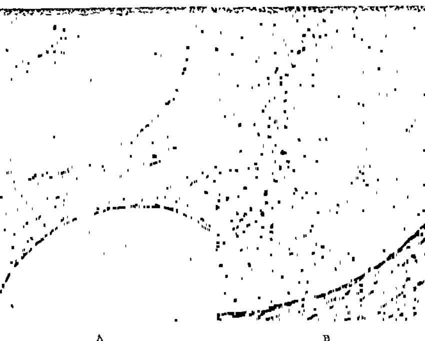


Fig 35—Post-necrotic scarring Man Nodule with normal lobulation Unaffected portal tracts in normal relationship to unaffected hepatic veins survive in the nodules circumscribed by the bands of scar tissue Laidlaw's reticulin stain A × 23, B × 44

portal tracts and veins (Figs 35, 36A). Such do not occur in diffuse hepatic fibrosis, for that lesion early affects every portal tract and central vein throughout the organ (Figs 8, 40) There can be no doubt that a lesion showing the features described by Mallory as 'toxic cirrhosis' is frequently found in man There is also no doubt that its characteristics are indistinguishable from those of the fibrosis following experimental dietetic necrosis In animals this lesion only develops after a preceding massive hepatic necrosis, and as such qualifies to be regarded as a distinct entity There would, therefore, appear to be no longer any valid reason for denying the same status to the identical lesion in man This is not to imply, however, that the presence of this lesion is proof that the necrosis from which it has developed was due to faulty nutrition

new formation of fibrous tissue and, as Mallory clearly recognized, in 'toxic cirrhosis' the bands of fibrosis arise mainly from the con-

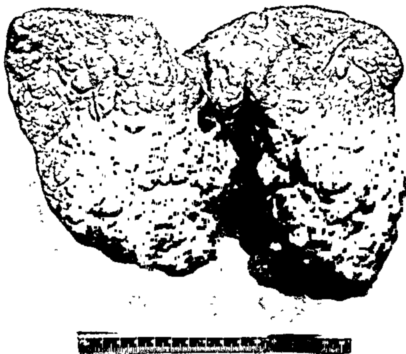


FIG 34—Post-necrotic scarring The liver is of normal size, studded with nodules of irregular size and intersected by fibrous scars Specimen from the male patient described on p 175 Compare with Fig 5

densation of existing, rather than from formation of new, fibrous tissue. These objections, however, could be overcome by simply calling the lesion what it is: post-necrotic scarring of the liver. More serious is the difficulty of distinguishing all cases from diffuse hepatic fibrosis Parenchyma, devoid of lobular structure, occurs in both conditions, but it is only in post-necrotic scarring after massive hepatic necrosis that areas showing normal lobulation are present. In typical cases such areas are found without difficulty. In others, however, the unorganized masses of parenchyma, formed by the hyperplasia of isolated groups of cells (Fig. 27, 36B), are so numerous that it is only after

lesion may occur after repeated attacks of zonal necrosis due to poisons, or it may develop on the basis of a heavy, prolonged, fatty, infiltration.



FIG 37—Diffuse hepatic fibrosis Man, alcoholic The liver is slightly enlarged and uniformly covered with fine granulations Compare with Fig 6

It is the latter which is relevant to the present considerations and in this, even when advanced, some degree of fatty infiltration is usually still present in the parenchyma.

Livers showing all the characteristics of diffuse hepatic fibrosis are frequently found at autopsies on human subjects (Figs 37, 38, 39). It is only recently, however, that their relationship to a preceding fatty infiltration has been appreciated (Fig 40) Mallory[42] regards such infiltration as of little significance, although he comments on the frequency with which this type of fibrosis is complicated by fatty change. Eppinger[15] dismisses the subject with the remark that fatty infiltration may be superimposed upon any kind of fibrotic liver But Connor[8,9] has brought forward strong evidence for regarding diffuse fibrosis in man as the sequel to such infiltration and has called attention to this view by naming the condition 'fatty cirrhosis'. The lesion described by Connor agrees in all its particulars with the diffuse fibrosis

Post-necrotic scarring develops after massive hepatic necrosis from any cause. Its occurrence in human cases, in whom there is no history of

A B

[illegible]

poisoning or infection of the liver, raises, however, the possibility that nutritional factors may have played a significant part in its causation

Diffuse Hepatic Fibrosis

Experimental, diffuse hepatic fibrosis is characterized by the uniformity of the lesion throughout the liver (Fig. 28) A fine fibrosis pervades the whole organ Every lobule is affected and, in the later stages, its architecture destroyed by penetrating fibrous strands. Hyperplasia follows, the isolated sections of the original lobule proliferating concentrically into masses without lobular structure, and, this process being general, a fine and more or less uniform granularity is produced throughout the organ (Fig. 29). Experimentally, such a

differences when found. Such differences are present in a far larger proportion of cases than is generally appreciated and, according to the care with which they are sought, the number of unclassified cases of hepatic fibroses will be reduced Over sixty years ago Sabourin classified hepatic fibroses into monolobular and multilobular types, and stated clearly their points of difference He writes,[88] 'Mais ce que différencie du tout au tout la cirrhose monolobulaire de la multilobulaire, c'est que, dans cette dernière, il y a une foule de petits domaines vasculaires portes et sus-hépatiques qui sont respectés par le processus cirrhotique, tandis que, dans la première, les deux systèmes sont pris au même degré jusque dans leur ramifications ultimes.' These are the essential criteria for distinguishing post-necrotic scarring and diffuse hepatic fibrosis respectively in experimental animals. More recently Rolleston and McNee[86] adopted, independently, a similar classification into multilobular, unilobular and intercellular types Their multilobular type is one in which the fibrous bands circumscribe many intact liver lobules, their unilobular, one in which such bands circumscribe single lobules; their intercellular, a condition in which young fibrous tissue surrounds the individual parenchymal cells. The latter is uncommon and in some instances, at least, is simply an early stage to one of the other varieties. It is seen in infants dying of congenital syphilis and in the early stages of subacute cholangitis. But the two former types are common and include most hepatic fibroses

The objection will undoubtedly be raised that, although multilobular fibrosis of the liver is common, 'acute yellow atrophy' is rare, and that it is obvious from clinical evidence that few cases of that type of fibrosis originate in this way. As long as the conception of acute massive necrosis is limited to its most severe and widespread form—'acute yellow atrophy'—this objection is valid But it has already been stressed (p. 5) that the term 'massive' applies only to the extent of the lesion *within* the individual lobule and has no bearing at all on the extent to which the liver as a whole is involved This acute massive necrosis may range from conditions in which practically the whole liver is attacked ('acute yellow atrophy') to those in which the lesion is limited to only a few lobules In the previous chapter the experimental condition of recurrent attacks of acute massive necrosis, affecting but few lobules on each occasion, has been described The clinical syndrome of subacute hepatitis has a similar pathology[294] which is evident in puncture biopsy performed in the early stages of the illness (Fig 52), although it may be obscured by widespread fibrosis when the patient

produced experimentally by means of diets which cause fatty infiltration of the liver; both are indistinguishable from classical 'portal cirrhosis'.

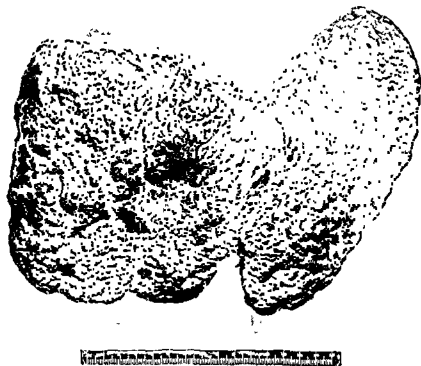


FIG 38—Diffuse hepatic fibrosis Man, alcoholic Late stage The liver is thin and somewhat atrophied Its surface is covered with small granulations

Hepatic Fibroses in General

It is thus possible to distinguish in man two clear types of hepatic fibrosis corresponding to the two types produced by dietary means in

[illegible]

is more apparent than real. The custom of grouping all kinds of widespread fibroses of the liver together under the single heading of 'cirrhosis' discourages the search for those points of difference upon which depends their differentiation, and it obscures the significance of these

differences when found. Such differences are present in a far larger proportion of cases than is generally appreciated and, according to the care with which they are sought, the number of unclassified cases of hepatic fibroses will be reduced. Over sixty years ago Sabourin classified hepatic fibroses into monolobular and multilobular types, and stated clearly their points of difference. He writes,[34] 'Mais ce que différencie du tout au tout la cirrhose monolobulaire de la multilobulaire, c'est que, dans cette dernière, il y a une foule de petits domaines vasculaires portes et sus-hépatiques qui sont respectés par le processus cirrhotique, tandis que, dans la première, les deux systèmes sont pris au même degré jusque dans leur ramifications ultimes.' These are the essential criteria for distinguishing post-necrotic scarring and diffuse hepatic fibrosis respectively in experimental animals. More recently Rolleston and McNee[36] adopted, independently, a similar classification into multilobular, unilobular and intercellular types. Their multilobular type is one in which the fibrous bands circumscribe many intact liver lobules, their unilobular, one in which such bands circumscribe single lobules, their intercellular, a condition in which young fibrous tissue surrounds the individual parenchymal cells. The latter is uncommon and in some instances, at least, is simply an early stage to one of the other varieties. It is seen in infants dying of congenital syphilis and in the early stages of subacute cholangitis. But the two former types are common and include most hepatic fibroses.

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comes to necropsy. The full implications of this syndrome for hepatic pathology have not yet been grasped, for, as yet, it is only the more rapid forms which have been clearly recognized, although it seems probable that more slowly progressing forms will prove to be even more common. It is in this process of recurrent attacks of acute massive necrosis, each limited to a few lobules, that the genesis of multilobular hepatic fibrosis, or the common form of post-necrotic scarring, will probably be found.

Very commonly, however, fibroses of the liver are seen which show features of both post-necrotic scarring and diffuse hepatic fibrosis Experimentally, similar lesions can be produced by diets which lead simultaneously to protein deficiency and to fatty infiltration. As will be seen later, comparable diets are habitually eaten by certain native races among whom hepatic fibroses are common. It is probable, however, that more commonly such mixed lesions arise on the basis of post-necrotic scarring. Minor degenerative changes and centrilobular necrosis can frequently be seen in the multilobular nodules in this condition, possibly because the circumscribing fibrosis interferes with blood supply to the nodule. In the normal liver, repeated centrilobular necroses are known to lead to the development of a diffuse hepatic fibrosis, and it seems reasonable to believe that they may have the same result within the multilobular nodules of post-necrotic scarring. A mixed lesion would then result. But such degenerative changes are not present in all nodules at the same time. Even in long standing cases, it is usually possible to find some in which the typical lobular structure is preserved and so to differentiate the lesion from a true *diffuse hepatic fibrosis*.

It thus seems that Mallory's 'toxic cirrhosis' is but an extreme example of 'multilobular cirrhosis', Connor's 'fatty cirrhosis' but a particular form of 'unilobular cirrhosis', and that the mixed types are either multilobular lesions on which a diffuse hepatic fibrosis has been superimposed, or the result of the operation of a complex of conditions each of which, when acting individually, gives rise to one or other lesion. If these views are correct, then the two prototypes of hepatic fibroses in general are post-necrotic scarring and diffuse hepatic fibrosis 'Multilobular cirrhosis' is post-necrotic scarring; 'monolobular cirrhosis'—although a misnomer, for the nodules are hyperplastic fragments of, rather than intact, lobules—is diffuse hepatic fibrosis. The implications are that the pathogenesis of the former lesion is to be sought in a preceding injury of such severity as to wipe out whole lobules and to give rise to a massive type of hepatic necrosis;

of the latter in a chronic infiltration, or in repeated minor injuries which are limited to a zone within the lobule.

DIETETIC FACTORS AS POSSIBLE CAUSATIVE AGENTS IN HUMAN DISEASES OF THE LIVER

It is evident that, under the conditions of Western civilization, circumstances are rarely such as to force human beings to subsist on diets comparable in deficiency to those required for the production of experimental liver injury in animals. When similar lesions occur in men living in temperate climates then some explanation other than a direct dietary deficiency must be sought. But in tropical [illegible]
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tha[illegible]

Massive Hepatic Necrosis, Post-Necrotic Scarring, and Primary Cancer of the Liver in the Tropics

In tropical and sub-tropical countries throughout the world, outbreaks of a severe type of jaundice are not uncommon [30 31 37 46 60 66 72 73] Clinically, the illness is similar to the infective hepatitis of the temperate zones save that it is often more severe, recovery is slow, and the immediate death rate high. In fatal cases, the liver shows massive necrosis Repeated investigations have established that this type of jaundice is not due either to yellow fever or to Weil's disease.[37] Although frequently attributed to malaria it occurs where malaria is not endemic.[46] It is often loosely called toxic jaundice, but no evidence of its consistent association with exposure to a particular poison or infection has been produced, and the designation seems to be simply [illegible]

[illegible]

countries where malnutrition is prevalent and, even then, only among the poorer natives. In epidemic form it may occur after a bad malarial season has reduced the community to poverty.[30] Dietary surveys in such countries reveal that the diet of the poorer classes is grossly deficient in protein [39 68 69]

In India a subacute hepatic necrosis is relatively common among children in the first three years of life. Until the investigation of Radakrishna Rao [50a] revealed its true nature, it was termed infantile biliary

† My friend, Dr H. C Trowell, of Uganda, put the matter succinctly by saying that if the patient recovered, the diagnosis was infective hepatitis, if he died, toxic jaundice [66]

cirrhoses. In the early stages it is characterized by enlargement of the liver, intermittent fever, and constipation; in the later by jaundice, splenomegaly and ascites. The condition occurs almost exclusively among the children of vegetarian Hindus.[47, 50] So far no toxic or infective factor adequate to account for its causation has been discovered, but it may be significant that the onset of the illness is shortly after weaning when the dietary is being changed from one rich to one poor in protein, and that the condition is commoner among the children of *the higher and stricter castes, such as the Brahmins, than among* lower classes of Hindus

In those countries where 'toxic jaundice' is common, 'tropical cirrhosis' is notoriously prevalent. A proportion of these cirrhotic livers are examples of post-necrotic scarring,[48] and examination of material obtained by puncture biopsy of the liver in living patients shows a similar incidence[66] But not all such cases can be related to a preceding illness with severe jaundice Nor is such a correlation necessary, for clinical experience, in temperate climes, shows that massive hepatitis may occur in a subacute form, and progress to post-necrotic scarring, without the patient ever being jaundiced. It seems, therefore, that *in countries where 'tropical cirrhosis'* is prevalent a proportion of such cases can be attributed to a preceding massive necrosis of the liver

Primary cancer of the liver is one of the rare neoplasms in races living under the conditions of Western civilization; but among certain tropical and Eastern races it is the commonest carcinoma.[3, 4, 70] Statistics in sixteen reports from tropical and sub-tropical Africa show an average incidence rate of 37·4% of all neoplasms, and in one report, concerning Bantu labourers, primary hepatic cancer was found in 90·5% of 253 consecutive cases of carcinoma.[3] That this high incidence is a function of environment rather than of race, is indicated by the fact that the negro in North America is no more subject to this cancer than the white population among which he lives.[36] It has long been recognized that primary carcinoma of the liver arises, almost invariably, in livers which are already cirrhotic,[29] and Muir [44] has pointed *out that it is particularly prone to develop in that type of hepatic fibrosis characterized by conspicuous nodular hyperplasia.* Comparison of the geographical distribution of primary carcinoma of the liver and 'tropical cirrhosis' shows that the two are associated [46] The relevance of these observations lies in the influence of diet upon the production of experimental primary cancer of the liver. Such can readily be produced in rats by dimethylaminoazobenzene (butter

yellow). Low protein diets facilitate, while high protein diets prevent, the development of this experimental lesion.[13]

It is thus evident that human beings living on deficient diets are prone to develop similar lesions to those which are produced in rats by similar dietary deficiencies. In the absence of any other explanation which would account for the nature, severity and geographical distribution of the human disease this association cannot lightly be dismissed But that is not to say that massive hepatic necrosis and its sequelae can be produced in man simply by dietary deficiency There is in fact no evidence that this is so On the contrary in the vast majority of human cases of acute and subacute massive necrosis there is good evidence that a positive agent, infective or toxic, is involved All that can be said is that, in chronically malnourished races, agents which normally produce only a mild and recoverable hepatitis, tend to produce a severe and fatal necrosis. As far as the evidence goes at present the role of dietary deficiency in relation to this type of liver lesion is to be sought, at least in the vast majority of cases, in aggravation rather than in initiation of disease.

Diffuse Hepatic Fibrosis in the Tropics

Since Matthew Baillie[1] first pointed out the association, cirrhosis of the liver in temperate climates has generally been attributed to indulgence in alcohol, and its relative rarity in children has been ascribed to their freedom from that vice. In tropical countries, however, the condition is common among native races who, because of poverty or religious scruples, are prevented from such indulgence, and in such races cirrhosis in children is also common. Evidence has already been brought forward that some of these cases are, in fact, post-necrotic scarring But only a proportion can be so explained The majority are classical examples of diffuse hepatic fibrosis, and the question arises as to their causation

As in the case of massive hepatic necrosis, so this diffuse hepatic fibrosis has been attributed to preceding attacks of various tropical illnesses but, with accumulating experience, the influence of these has been steadily discounted. The parasitic fibroses have been distinguished by their peculiar morbid anatomy, the importance previously attributed to repeated attacks of malaria has been weakened by the failure to correlate the incidence of hepatic fibrosis with the prevalence of that fever. But looking at its distribution throughout the world one correlation emerges Diffuse hepatic fibrosis in the tropics is correlated with poverty and, through that, with malnutrition.

In recent years considerable attention has been paid to a syndrome

variously known as Kwashiokor,[11a 67 77 78 79] malignant malnutrition[58 68 69] and as infantile pellagra.[21 23 24 34] It was first recognized in central



FIG 39—Diffuse hepatic fibrosis Man Specimens from three livers showing, from left to right, successive stages in the development of the lesion Compare with Fig 29

Africa, but closely similar conditions occur in India[17a] and the West Indies.[74 74a] The condition occurs both in adults and children, but it is particularly common and attains its more dramatic forms, in the latter. In the fully developed African type the patients show oedema, streatorrhoea, various dermatoses, macrocytic anaemia,
In children,
If untreated
uietly. The
African condition is probably a complex of several syndromes, and in other places some of these may be absent. But an invariable and special pathological feature of the condition is the grossly fatty liver (Fig 40A) In this the fatty infiltration is often so marked that *microscopic sections of the organ can only be distinguished from adi-*

pose tissue by the presence of portal tracts. Rarely such cases have been reported from temperate climates. In the recent famines in Europe a

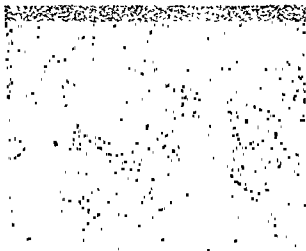


Fig 40 A

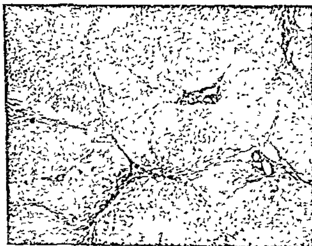


Fig. 40 B

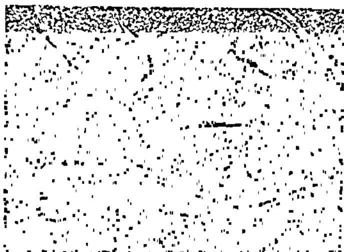


Fig 40 C

Fig 40—Diffuse hepatic fibrosis Man Series showing the development of the lesion from the stage of fatty infiltration Laidlaw's reticulin stain All × 30

A Fatty infiltration of the liver
B Fine bands of connective tissue are forming and linking up the hepatic veins with each other and with the portal tracts
C Late stage The organ is intersected with numerous bands of connective tissue which link the vascular tracts and isolate areas of lobular paren-

condition in malnourished infants characterized by oedema and an enlarged fatty liver has been observed.[10, 71] Graham[27] reported a series of cases of sudden death in young adults in Baltimore, in whom, at autopsy, the only abnormality was the great amount of fat in the liver. The further sequence of events in these cases has been followed by the Gillman brothers[22] who have demonstrated, by means of the liver puncture-biopsy technique, the gradual evolution from gross fatty infiltration of a diffuse hepatic fibrosis (Fig. 40). There can thus be no doubt that in man, as in experimental animals, heavy, prolonged,

dent upon the habitual consumption of a deficient diet. It affects only those native races who are malnourished and then only the poorer classes It is particularly prone to develop after weaning while the growing infant is getting adjusted to the coarse deficient diets of his elders. In Western civilization, it is seen to attack previously healthy

Such fatty infiltration of the liver cannot be due to an excess of dietary fat, for under all the above conditions the diet is, by ordinary standards, poor in this respect. The conclusion seems inescapable that the infiltration is due to lack of some substance which normally prevents the accumulation of fat in the liver. Such a deduction would accord with the observation that the maximum incidence of the condition is in the growing child for, as has been shown already, growth increases the need for lipotropic factors. This effect of growth has actually been demonstrated for one of the native diets. On the Rand the basis of the native diet is a porridge of mealies and some sour milk. If rats are given the porridge alone they neither grow nor develop fatty livers But if a supplement of a little sour milk is given growth occurs and the liver lesions appear [20, 25] The effect of larger supplements of milk was not tried but, judging by the experiments of others, they would have

due to a deficiency of lipotropic factors in their diet.

Gillman and his colleagues, advanced cases of South African type are not relieved by small doses of such strong lipotropic factors as methionine and yeast Riboflavin was also without effect, but the condition was ameliorated by liver extract and cured by oral administration of powdered hog's stomach [24] But it has recently been reported that the milder, and apparently less complicated, condition of oedema and fatty infiltration of the liver, which occurs in the West Indies is cured by adequate supplies of milk [74, 74a] It must be remembered, however, that, when dietary protein is low, many other essential nutriments are low also.

On the basis of animal experiments it is possible that fatty infiltra-

tion of the liver in man may arise from several deficiencies. But the most obvious deficiency in the diet of races subject to this condition is protein and a clear correlation can be seen to exist between the consumption of such diets and the prevalence of infantile, diffuse, hepatic fibrosis. In East Africa,[68, 69] and South Africa,[23, 24, 25] and the West Indies,[74] the condition is common and the correlation clear. The recent famines in Europe were characterized by a deficiency of protein. This was particularly marked in Budapest, and there the hospitals for children were filled with cases who, at death, showed gross, fatty infiltration of the liver. When milk and meat again became available the condition disappeared My friend, Professor Veghelyi, informs me that three of the children, who had suffered from this condition two to three years ago, have since died from accident or intercurent infection. All showed diffuse hepatic fibrosis.

'Alcoholic Cirrhosis of the Liver'

Despite repeated attempts to demonstrate that the group of conditions known as cirrhosis of the liver is caused by alcohol, the utmost that has been established is that 'cirrhosis' is somewhat more common among alcoholics than among abstainers,[15, 33, 51] and it is now generally admitted that alcohol is, at most, a contributory factor in the pathogenesis of this lesion.

Pathologists and clinicians have long recognized that, although 'portal cirrhosis' is the common lesion in advanced alcoholism, fatty infiltration of the liver is the usual finding in the early stages.[52] Nearly a century ago Rokitansky [54] wrote. 'The latter (adipose deposit) may be the primary affection upon which the granular disease is grafted in the shape of cirrhosis ' So impressed were the French clinicians of the nineteenth century with this sequence in alcoholics that they distinguished at an early stage a 'steatosis' of the liver, when the organ was enlarged and fatty, from a later stage of 'cirrhosis', when it was shrunken and atrophic.[64] It is this type of atrophic liver, covered uniformly with fine granulations (Figs 37, 38), rather than the irregularly scarred, grossly nodular organ, which is particularly found in chronic

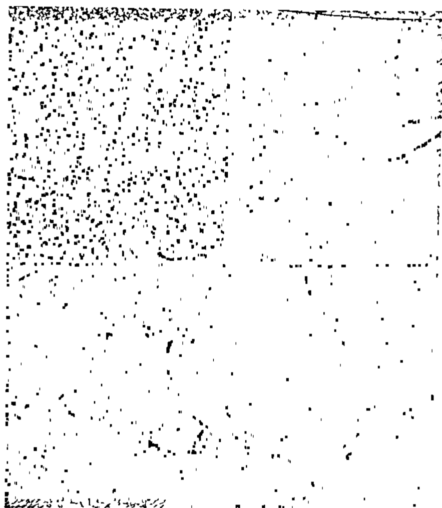
nuts . . . none of the granulations are larger than a hemp seed. Connor [8, 9] distinguishes three stages in its development. The first is found in patients who have been drinking excessive amounts of alcohol for only a few months. In them the liver is large, pale, greasy

and smooth; and on microscopic examination shows gross infiltration with fat, but no fibrosis The second occurs when alcoholism is of several years duration. The liver is still large and fatty but a fine fibrosis is developing from the vessels. The third and last stage is seen in chronic drunkards The organ is now small and fibrosed and usually contains little, if any, excess of fat It is a typical diffuse hepatic fibrosis. From his knowledge that fatty infiltration of the liver was an essential factor in the production of experimental hepatic fibrosis in dogs,[6, 7] Connor saw clearly that it was of equal importance in the pathogenesis of a similar lesion in alcoholics. The sequence of microscopical changes is shown in Figure 41 It is evident that they are closely similar to, if not identical with, those produced in rats by diets causing heavy fatty infiltration of the liver, and those seen in human cases of Kwashiokor who have never tasted alcohol.

Consideration of the nutritional aspects of alcoholism indicates how such a preceding fatty infiltration could be brought about, and maintained Alcohol contains no lipotropic factors. In excess it produces gastritis, impairs appetite and so limits the addict's intake of food Further, alcohol is expensive and so are the foods rich in lipotropic factors and protein. All these factors tend in the same direction, to the ingestion of a deficient diet such as would lead to the development of a fatty liver and subsequent diffuse hepatic fibrosis. Whether alcohol itself can contribute to the development of this lesion by a direct toxic action on the liver cells is still unsettled. But, even if it can, it appears that such a contribution is gratuitous and that the observed association of fibrosis of the liver with alcohol can more readily be explained as a result of the malnutrition consequent upon alcoholism. Such an explanation would be compatible with the observation that diffuse hepatic fibrosis is not limited to alcoholics and, even among them, is more common in the poor than in the rich.

It would be unjustifiable to conclude that diffuse hepatic fibrosis is the only fibrotic lesion of the liver which can occur in alcoholics In temperate climates it is the commonest type, and it is possible that future statistical research will reveal a correlation between the incidence of this particular form of hepatic fibrosis and the prevalence of alcoholism, such as it failed to establish for cirrhosis of the liver in general. The deficient diets consumed by the alcoholic lacks, however, not only specific lipotropic factors, but protein in general The occasional discovery of post-necrotic scarring in an alcoholic need, therefore, cause no surprise.

A B



C D

Fig 41

A [illegible] B, C, D,

[illegible]

duration

B [illegible]

C [illegible]

commencing to link the two

D Man, aged 56 years, bartender by occupation Had been drinking steadily for many years. Fully developed diffuse hepatic fibrosis.

SECONDARY NUTRITIONAL DEFICIENCY AS A POSSIBLE CAUSE OF LIVER DISEASE

It is a truism that nutritional deficiencies occur when the require-

especially high incidence of fatty infiltration of the liver and diffuse hepatic fibrosis in growing children has already been ascribed, in part, to the increased requirements for liptropic factors during growth.

Pregnancy

The predisposition of pregnant women to develop clinical conditions due to vitamin deficiency is well recognized and is attributed to a natural provision by which the nutritional demands of the foetus are satisfied even at the expense of the mother's health. If, in addition, the maternal diet is faulty, or absorption of food is curtailed by anorexia or vomiting, development of a deficiency disease may become inevitable It would not, therefore, be surprising if hepatic lesions, similar to those caused in experimental animals by dietary deficiency, proved to be unusually common during pregnancy

Three lesions of the liver have been described as occurring in pregnant women, fatty infiltration, periportal haemorrhagic necrosis, and massive hepatic necrosis Fatty infiltration of the liver, sometimes with centrilobular necrosis, is particularly associated with the pernicious vomiting of pregnancy[56, 80] An analogous condition can easily be produced in animals If rats are given a diet containing just sufficient casein and choline, to prevent fat accumulating in the liver, and then allowed to become pregnant, gross fatty infiltration of the liver develops After parturition the fat content returns to the normal level and this, perhaps, explains why in such animals diffuse hepatic fibrosis does not develop The periportal necrosis associated with eclampsia

although still *in situ*, were degenerating or dead, and blood was pooled in the periportal zone.

In temperate climates massive hepatic necrosis is not common but, in general, it affects females more often than males. This, as French's first pointed out,[18] is largely due to the number of cases in pregnant

women,[15,32,56,80] thus, of 164 cases in women, 66 were in-patients who were either pregnant or suckling[32] But the infants from such cases have no hepatic lesions. When one considers the preference enjoyed by the foetus in the matter of nutriments available for both mother and child a possible explanation of these observations becomes apparent.[47a]

Thyrotoxicosis

Reference has already been made to the finding of liver lesions in thyrotoxic patients[2,5,41,75] These include fatty infiltration, diffuse hepatic fibrosis, massive hepatic necrosis and post-necrotic scarring. The increased nutritional requirements, consequent upon the raised metabolic rate in these patients, may well contribute to their development.

Amino-aciduria

Excessive amounts of amino-acids are known to be excreted in the urine in three conditions: in the terminal stages of massive hepatic necrosis, in hepato-lenticular degeneration,[70a] and in the rare condition called the de Toni-Fanconi syndrome[13,16,17,40] In the first, the amino-aciduria is associated with an increased level of amino-acids in the blood and is believed to be due to autolysis of dead liver cells. In the two latter the amino-acid level in the blood is not raised, and there is further evidence which also suggests that the amino-aciduria in these cases is due to an abnormality of renal function.[12,61]

The fully developed de Toni-Fanconi syndrome[13,14,17] is characterized by renal glycosuria, hypophosphataemic rickets or osteomalacia, enlargement of the liver and spleen, and amino-aciduria. An inconstant association with cystinuria has been noted[40] and in these cases cystine crystals have been found in the reticulo-endothelial system. The condition is familial and, even when it does not produce disabling symptoms until adult life, its earlier presence is indicated by the stigmata of rickets. It does not affect all members of the family and in those affected does not always appear as the full syndrome. It seems, from personal observations and the published accounts, that the hepatic lesions and splenomegaly only develop in those cases with amino-aciduria. At autopsy hepatic lesions ranging from acute massive necrosis to fibrosis have been recorded. In two cases observed personally, post-necrotic scarring and nodular hyperplasia were present

(Figs 42, 43). Both also had developed primary cancer of the liver. One was a child of ten years of age

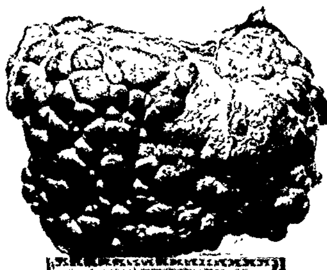


Fig 42—Post-necrotic scarring and nodular hyperplasia from a man, aged 34 years, with the adult form of the de Toni-Fanconi syndrome Carcinomatous change was present in one of the nodules on the posterior surface

In view of the reported association with cystinuria, and the known relationship between experimental [illegible]
scarring, it was expe[illegible]
showing this kind o[illegible]
detect any excess in [illegible] patients available In all, excessive quantities of a mixture of amino-acids was excreted in amounts of 16 g. daily, and in this mixture valine, glycine, alanine and serine were present in relatively large amounts. In addition a considerable quantity of peptide, composed of serine and glycine, and the amino-acid α amino-n-butyric acid [124] were present [13] At first sight these findings would seem inadequate, either quantitatively or qualitatively, to account for the hepatic injury on the basis of an amino-acid deficiency consequent upon loss of such acids in the urine Perhaps a clue is provided by the excretion of serine which, in the free state and in combination as a peptide, may amount

to over 2 g daily.[12] Now the major portion of the cystine required in the body is formed from methionine, and for this process serine



FIG 43—Post-necrotic scarring and primary carcinoma of the liver from a female child, aged 10 years, with the de Toni-Fanconi syndrome Dr Donald Hunter's case

is necessary.[14] Serine is not present in large quantities in dietary protein but, not being an essential amino-acid, can apparently be synthesized in the body. If the loss in the urine approached the combined amount available from ingestion and synthesis, a serine deficiency would be produced, and this could entail a failure to synthesize sufficient cystine. Under such circumstances massive hepatic necrosis and its sequelae might well be produced.

Hepato-lenticular degeneration, or Wilson's disease, is a familial disease characterized by a lesion of the liver and changes in the nervous system which are particularly marked in the putamen. Denny-Brown[15]

describes the hepatic lesion as follows: 'The condition is the multiple nodular hyperplasia of Marchand, the toxic cirrhosis of Mallory or the healed yellow atrophy of other authors. It may vary in degree from changes typical of subacute hepatitis to a chronic stage. . . .' Recently Uzman and Denny-Brown[108] reported the finding of persistent amino-aciduria in early cases of this condition before liver function tests revealed any evidence of liver damage and puncture biopsy of the liver showed only swollen parenchymal cells without fibrosis Dr C. E. Dent in my own laboratory has confirmed the presence of persistent amino-aciduria in three established cases but detailed study of the individual amino-acids present in the urine has not been completed

As yet the exact biochemical consequences of the chronic loss of amino-acids in the urine in the de Toni-Fanconi syndrome and in Wilson's disease are not yet clear But the over-riding consideration would seem to be that, in the only two clinical conditions yet known in which there is persistent amino-aciduria, hepatic lesions identical with those of experimental protein deficiency occur. The possibility would, therefore, appear to be strong that the mechanism of these conditions will prove to be some disturbance of amino-acid metabolism focused on the same point as the experimental dietetic deficiency

METABOLIC DISORDERS PRODUCING DIFFUSE HEPATIC FIBROSIS

Hitherto consideration has been limited to those cases of diffuse hepatic fibrosis which might be explained on the basis of direct, or indirect, nutritional deficiency. But nutritional deficiencies exert their influence by affecting metabolism and it is, therefore, to be expected that related disorders of metabolism due to disease may themselves lead to similar effects Actually, one of the first observations on experimental diffuse hepatic fibrosis was that this lesion developed in depancreatized dogs[8] The occurrence of a similar lesion in human subjects with diabetes mellitus had long been established[8,9] In both cases the lesion develops on the basis of long-standing fatty infiltration of the liver, and does not occur if this infiltration is prevented. But diffuse hepatic fibrosis also occurs after infiltration with substances other than neutral fat. It is seen in glycogen disease.[11,33] It is invariably present in adult cases of Gaucher's disease (Fig 49) It has been reported in primary xanthomatosis and the Nieman-Pick syndrome[18,49,63] Occasionally its early stages can be detected by microscopic examination in cases of amyloid disease, but such patients rarely live long

enough to develop the full lesion. All these different disorders have one point in common. They are all conditions in which the liver cells are distended by some substance which accumulates in their cytoplasm. Diffuse hepatic fibrosis seems, therefore, to be a reaction to infiltration as such rather than to any particular infiltrating agent; its development can be adequately explained on the basis that all infiltrations interfere with the intralobular circulation and so lead to malnutrition and degeneration of the parenchyma.

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CHAPTER V

NOXIOUS FACTORS CAUSING LIVER INJURY

It has long been known that necrosis of the liver, both in man and in experimental animals, can readily be produced by certain chemicals. Such are, in general, protoplasmic poisons, capable of directly killing any cell with which they come in contact, and the hepatic lesion they produce can reasonably be explained as the direct expression of their action on the liver parenchyma. For many years this was the only kind of hepatic necrosis for which a causal relationship could be established and it is not, therefore, surprising that the conception of the toxic origin of hepatic necroses, in general, was extended until it came to dominate this field of pathology. Hepatic necroses, occurring in the course of febrile illnesses, were regarded as probably due to the action of a hypothetical toxin produced by living organisms. The necroses in pregnancy were assumed to be the result of a toxaemia. More difficult to explain were the necroses in thyrotoxicosis, but suggestions were not wanting that even these were essentially toxic in origin. Eventually the position was such that the finding of a hepatic necrosis, whose origin was obscure, was almost automatically assumed to indicate the presence of some unknown liver poison. This assumption was not seriously challenged until the discovery of dietetic necrosis. But it has already become evident that a sharp classification of hepatic necroses into those due to the presence of a noxious agent, and those due to the absence of an essential nutriment, is not possible. The action of some poisons is profoundly modified by nutrient factors, the action of others may conceivably be due to their causing malnutrition. The problem of the hepatic necroses associated with exposure to poisons or infective agents is, therefore, by no means simple. It can best be approached by consideration of the experimental data.

EXPERIMENTAL HEPATIC NECROSES ASSOCIATED WITH POISONING

The experimental necroses associated with administration of chemical poisons, whether these are of synthetic or vital origin, are of two broad types, those in which the lesion follows shortly upon exposure to the poison, those in which its development is delayed, even though

exposure continues, for many days or weeks.[45] For convenience of discussion these will be distinguished as 'Immediate' or 'Delayed' hepatic necroses. Generally speaking, each of these clinical types corresponds to a different pathological form; immediate hepatic necroses being associated with zonal necrosis, delayed with massive necrosis. The sequelae in each are those of the respective anatomical forms of necrosis.

Immediate experimental hepatic necrosis

This lesion can be readily produced by a variety of synthetic chemicals and naturally occurring poisons. It is the lesion produced by the chlorinated hydrocarbons,[14] tannic acid,[16] phosphorus, and allyl formate[42 86] It occurs after injection of the endotoxin of Proteus vulgaris, extracts of certain algae,[2] or ingestion of poisonous mushrooms.

Carbon tetrachloride poisoning can be taken as a typical example. Within a few hours after the poison has been given, the animals fall ill. All the animals are affected and at about the same time. The illness is at its height twenty-four to forty-eight hours after the poison has been given and, at this stage, the liver shows, macroscopically, a general exaggeration of the lobular pattern and, microscopically, a centrilobular necrosis (Figs. 1 and 17) involving every lobule throughout the organ[13] During the next two or three days clinical recovery sets in and by the end of the first week the animal appears entirely normal. Traces of residual damage to the liver may, however, persist for a week or so longer. Even when the illness is at its height there is no clinical evidence of jaundice, oedema, or effusions into serous cavities. But for the findings at autopsy the presence of a hepatic lesion would rarely be suspected

This is the picture when a single injection of carbon tetrachloride is given by the natural routes of ingestion and inhalation, or by subcutaneous injection. With other poisons the clinical picture is similar, but the position of the necrosis within the lobule may be different. After chloroform, tannic acid or mushroom poisoning, it is also centrilobular; after allyl formate, phosphorus or the endotoxin of Pro- vulgaris, it is periportal (Fig. 18.)

Comparison of the immediate hepatic necrosis due to poisoning with dietetic necrosis

Comparison of the clinical histories of these immediate toxic with dietetic, experimental, hepatic necroses reveals three broad differences.

First, there is a marked difference in the time required for the illness to appear. Second, in immediate necrosis all the animals become ill at the same time, in dietetic necrosis the illnesses of different members of one group may be days or weeks apart. Third, the sequelae are different Animals surviving a single attack of immediate necrosis recover completely. After a single attack of dietetic necrosis a chronic hepatic lesion remains, and death, either in an acute attack or as a result of its sequelae, is the rule[46]

However much dietetic and immediate necrosis due to poisoning may differ, they are both, at their onset, acute illnesses of sudden development. It is, therefore, all the more striking that the latent period in the two conditions is so different In dietetic necrosis the latent period is measured in weeks, during the whole of which time the animal appears healthy although exposed to conditions necessary for the production of the illness. In immediate necrosis, on the other hand, the latent period is measured in hours. These differences are readily explained by the different causative mechanisms in the two conditions In dietetic necrosis the latent period is the time required for the state of deficiency to develop Naturally this varies with the poverty of the diet in protein, the success of the individual animal in obtaining food from the common supply, and the stocks of body protein in the animal at the beginning of the experiment. As a result the length of the latent period varies not only between animals on different diets but between animals in the same group But until the deficiency state develops the liver cells are normal, when it has occurred necrosis follows and in a few hours illness is manifest In immediate necrosis due to poisoning, however, the appropriate internal state is at once created by the introduction of the noxious agent into the body. There is, therefore, little variation in the length of the latent period between animals in the same group Thus the animal with immediate necrosis is in a similar position, immediately after receiving the poison, to the animal about to develop dietetic necrosis after several weeks on a deficient diet, and in the next few hours the symptoms of acute hepatic necrosis appear in both[45]

The pathological features of the two conditions show equally striking differences In dietetic necrosis[36] the lesion is massive in type (Figs. 25, 26 and 27), irregularly distributed, and the extent to which the different lobules are involved ranges from death of all parenchymal cells to unscathed survival In immediate necrosis, on the other hand, the typical lesion is zonal (Figs 1, 17 and 18), and effects every lobule throughout the liver in the same fashion and to approximately the

same extent.[13] In dietetic necrosis scarring of the liver invariably follows even the mildest attack. Such scarring occurs at the sites of previous necroses and, these being irregularly distributed, the final result is the grossly distorted liver of post-necrotic scarring (Fig. 5) in which bands of fibrous tissue cut into the organ and separate areas in which fibrosis has not occurred (Fig. 7). In immediate hepatitis following poisoning the subsequent course depends upon whether the attack is single or repeated. If single, complete restitution to normal takes place; if repeated, a uniform diffuse hepatic fibrosis develops.[14]

There is, however, one variant of zonal necrosis which can lead to a different sequel. If the poison reaches the liver in exceptionally high concentrations, as after intraportal injection,[15] or if it is of unusual virulence, as in the case of the toxins of some poisonous fungi,[26] then the resulting zonal necrosis may be so extensive as to involve the whole lobule. In that case it is virtually massive in type and its sequelae are those of that anatomical form. But the illness still has the short latent period and other clinical features of immediate necrosis and thereby can be differentiated from delayed necrosis due to diet or certain special poisons.

Delayed experimental hepatic necrosis

It is a striking fact that, although poisons which lead to immediate hepatic necrosis in man readily cause similar lesions in experimental animals, those poisons which are associated with delayed necrosis in human patients rarely reproduce this lesion in experimental animals. Cinchophen, for example, which may lead to the delayed development of massive hepatic necrosis in man fails to produce any significant liver damage in animals.[51] Similarly, trinitrotoluene is without effect on experimental animals kept under normal conditions.[60, 61] Indeed, the only clear example of delayed experimental necrosis, caused by noxious agents, is that due to selenium, and, as yet, selenium necrosis of the liver in man has not been recorded. Fortunately, however, selenium poisoning in animals has been so extensively investigated

[illegible]

scarring and in some animals is limited to the left lobes. Experimental

selenium poisoning has thus the clinical and pathological features of dietetic massive necrosis due to an incomplete deficiency of sulphur-containing amino-acids and, like that lesion, it is prevented by supplements of casein, methionine or cystine The explanation is suggested by the finding that, in the protein of plants grown on seleniferous soil, selenium has replaced sulphur in the sulphur-containing amino-acids. If, as seems likely, such acids are not utilisable by the body, then the poisonous action of selenium would be due to its leading to a deficiency of sulphur-containing amino-acids.

A similar explanation may account for the delayed development of massive hepatic necrosis in persons exposed to trinitrotoluene. This substance has no effect on animals receiving normal diets containing adequate amounts of protein.[60 61] Typical delayed hepatic lesions can, however, be produced in animals receiving low-protein high-fat diets[44] Trinitrotoluene combines with amino-acids, the free nitrous group linking with the amino group of the acid.[*] There is evidence that it raises the metabolic rate and thus the requirements for protein.[44] The combined influence of these two properties will tend steadily to produce a deficiency of amino-acids within the body. The role of dietary fat in facilitating the development of massive necrosis after ingestion of trinitrotoluene may simply be related to the solubility of that substance in fat, which might facilitate its absorption and does hold it in high concentration in the fatty infiltrated liver[47]

The concept that certain poisons may act by producing conditioned nutritional deficiencies bears on a mechanism of the liver concerned with detoxification. Potentially toxic substances may be rendered innocuous in one of three ways, by destruction, by alteration, or by combination with some metabolic factor to form a harmless compound If the organ is undamaged, substances dealt with by the two former methods would be innocuous even when given in large amounts. But those dealt with by the latter method could be capable of producing injury even in the normal animal Whether they do so or not would depend upon the dispensability of the particular metabolic factor with which they combine If this is not essential to metabolism, or can be produced in unlimited quantities, no harm results If, however, it is essential, and its supply is limited as would be the case if it were an essential amino-acid, then a dangerous state of deficiency would follow Under certain circumstances, therefore, the process of detoxification may be a liability rather than an asset. This suggestion need occasion no surprise for there is no reason to regard detoxification by combination as necessarily a special process evolved for a benignant

purpose It could equally well arise as the inevitable, and incidental, result of the production, along *the normal lines of metabolism,* of a compound which is incapable of being further broken down in the body.

Thus delayed hepatic necrosis from poisons resembles, clinically and pathologically, the type of massive necrosis produced by protein deficiency. Consideration of its possible causation suggests that the mechanism of the two may be fundamentally the same, the production of a nutritional deficiency.

FACTORS MODIFYING EXPERIMENTAL IMMEDIATE HEPATIC NECROSIS DUE TO POISONING

Dosage

It has already been mentioned that when a poison is injected into the portal vein, in order to ensure its reaching the liver in high concentrations, the resulting necrosis is so severe as to take on the character of a massive necrosis.[15] When administration is confined to more usual routes, dosage naturally influences severity. But this is less than might be expected. Thus in the rat, 0·016 c.c. of carbon tetrachloride per Kg. of body weight, when given subcutaneously, produces minimal lesions,[14] but there is very little difference in severity between the necrosis produced by 0·05 c c. and 1·7 c c. per Kg. The same consideration applies to rabbits and, indeed, in them it has been found impossible to produce death of all the liver parenchyma even when enormous doses have been given subcutaneously.[47] The correlation between the severity of the lesion and the dose of the causative poison is only approximate and above a certain minimum the dose may be varied within wide limits without producing any appreciable alteration in the extent of the necrosis. It is, therefore, all the more interesting that by other means, even when the dose of poison is maintained *constant, wide variations in severity can be produced.*

Nutrient Factors

The early observations were concerned mainly with the effects of carbohydrate and of fat, and it was found that diets rich in carbohydrate reduced, while diets rich in fat increased, the susceptibility to chloroform poisoning.[23, 24, 75, 78] Later, a correlation between resistance to such poisons and a high glycogen content in the liver was demonstrated.[37] This observation seemed, at that time, to explain the increased

susceptibility found in starvation, and when fatty infiltration of the liver had been produced by a high fat diet, for in both instances the liver is poor in glycogen. The protective action of carbohydrate was thought to derive from its ability to reduce the normal breakdown of protein and hence to conserve to the body the protein stores that were so vitally needed when liver cells were being destroyed by necrosis.[71, 81, 35, 32] The possibility of its forming harmless glycuronates with suitable poisons was also suggested.[82] Whether these explanations were correct or not is now doubtful but, at least, they served to direct attention to the importance of protein in this connection

It is mainly to Whipple and his school that we owe the mass of evidence which has established that susceptibility to chloroform, as measured both by the death rate and the extent of the zonal necrosis, is closely connected with the state of protein metabolism in the body[43, 44] Protein depletion greatly increases susceptibility, remedying such depletion restores susceptibility to normal. Searching for the explanation of this observation it was found that protein depletion leads to a fall in the total sulphur content of the liver,[47] and that the relative resistance to chloroform anaesthesia of pups, born of protein depleted mothers, could be correlated with the relatively higher sulphur content of their livers.[105] On the basis of these findings the effects of giving sulphur-containing amino-acids was tested, and it was found that methionine, cystine, and cysteine, but not choline, afforded definite protection against chloroform to protein depleted dogs.[85] Such measures also restore the lowered sulphur content of the liver to normal provided that their institution is not delayed for more than four hours after anaesthesia. But the most remarkable feature of these experiments is the speed with which administration of protein, or sulphur-containing amino-acids, restores normal susceptibility to dogs depleted of protein. It is surprising enough that administration, immediately before, or during, chloroform anaesthesia is sufficient It is little short of astonishing that injections of methionine, or cystine, as late as three to four hours *after* chloroform anaesthesia, are equally effective.[87]

To explain their results Miller and Whipple[87] suggest that the injury done to the liver cell may be due to chloroform disturbing an enzyme system, such disturbance being reversible for a period of three to four hours after its inception This enzyme system is, they suggest, rich in sulphydryl groups and they explain the protective action of the sulphur-containing amino-acids by their promoting the formation of such groups. But this protective action is only found in dogs previously

depleted of protein; it does not occur in normally nourished animals. If, as they imply, chloroform acts by reducing the number of effective sulphydryl groupings in an enzyme system, then it is difficult to see why the sulphur-containing amino-acids, when given during, or shortly after chloroform anaesthesia, should be able to augment the number of such groupings only when that number had previously been reduced by protein depletion. It would have been expected, if the suggestion were correct, that, given sufficient protein, normally nourished animals would be entirely protected from the effects of chloroform. Such is not the case.

It can hardly be a coincidence that the amino-acids which govern susceptibility to chloroform poisoning are the same as those which protect against dietetic necrosis of the liver; and any explanation of their protective action must seek to account for this association. It is also desirable that the same explanation should account for the other two factors which increase susceptibility to chloroform: anoxia and hyperthyroidism. The following explanation is suggested.

When considering the effects of experimental ischaemia upon the hepatic parenchyma it was noted that the first evidence of necrosis appeared about six hours after arrest of the circulation. After poisoning with the chlorinated hydrocarbons, no change is seen in the parenchyma until some two to four hours later. Then the parenchymal cells are seen to be swollen [103] But it is not until a further six to eight hours have elapsed that unequivocal centrilobular necrosis appears.[14, 103] This necrosis has already been attributed to the swollen parenchymal cells impeding the flow in the intralobular sinusoids to such an extent as to starve the more centrally placed cells of those blood-borne factors which are essential to life (Fig. 19). It is suggested that in protein depleted animals the parenchymal cells are so depleted of sulphur-containing amino-acids that they are dependent, from minute to minute, on the amount of these substances in the blood which circulates past them. Under these circumstances the slightest retardation of [illegible]

containing amino-acids are given at any time before this, they can reach all parts of the lobule in adequate concentrations, remedy the depletion, and so reduce the extent of the necrosis to that which is inevitable even in well-nourished animals. Such an explanation reconciles the effect of protein depletion in inducing dietetic hepatic necrosis with its other effect of exaggerating zonal necrosis due to poisons. It suggests

that such an exaggeration, whether caused by protein depletion, by anoxia, or by hyperthyroidism, has a common basis in the actual or relative inadequacy, under the particular circumstances, of the intralobular circulation to supply the needs of those zones of parenchymal cells which are normally spared. It indicates why poisons, like arsphenamine, which must be given in huge doses to produce even minimal lesions in normal animals,[49] readily cause 'immediate' centrilobular zonal necrosis in animals on diets deficient in protein.[63] It explains why it has not been possible to prevent entirely the centrilobular necrosis of chloroform poisoning by giving an excess of protein The integrity of the hepatic parenchyma is dependent upon several blood-borne factors. Ischaemia deprives it of all.

THE PATHOGENESIS AND CLASSIFICATION OF HEPATIC NECROSES IN GENERAL

It is opportune now to review the problem of hepatic necroses in general for it is evident that some of the older conceptions are no longer tenable

Necrosis of the hepatic parenchyma can be produced in one of two ways, by the presence of noxious agents or by the absence of some factor essential to cellular life The noxious agents can be chemicals or, as will be seen later, living organisms The factors essential to cellular life may be nutriments or oxygen. Uncomplicated examples of either type of necrosis can be produced experimentally but, in the majority of cases commonly attributed to poisoning, both participate to a variable degree It is, therefore, inaccurate to regard all necroses after exposure to noxious agents as 'toxic necroses', or all those due to lack of an essential factor as nutritional To meet these difficulties the adjectives 'Toxipathic' and 'Trophopathic' were introduced.[45] A toxipathic lesion is due to the direct action of a noxious agent, be that a chemical or a living organism A trophopathic lesion is one due to deprivation, directly or indirectly, of a factor essential to cellular life, be that oxygen or a nutriment It may well be that when these lesions can be discussed in terms of intracellular chemistry the distinction between them, and the need for distinguishing each by a separate term, will disappear But in the meantime the distinction appears useful. Thus the lesions of phosphorus or allyl formate poisoning are examples of uncomplicated toxipathic necroses; those due to cystine deficiency of a pure trophopathic process. The lesion in chloroform poisoning could be precisely, if pedantically, described as a tropho-

depleted of protein; it does not occur in normally nourished animals. If, as they imply, chloroform acts by reducing the number of effective sulphydryl groupings in an enzyme system, then it is difficult to see why the sulphur-containing amino-acids, when given during, or shortly after chloroform anaesthesia, should be able to augment the number of such groupings only when that number had previously been reduced by protein depletion It would have been expected, if the suggestion were correct, that, given sufficient protein, normally nourished animals would be entirely protected from the effects of chloroform. Such is not the case.

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[illegible]

even in well-nourished animals. Such an explanation reconciles the effect of protein depletion in inducing dietetic hepatic necrosis with its other effect of exaggerating zonal necrosis due to poisons. It suggests

necrosis, if the attack is single, is followed by complete recovery; if frequently repeated, a diffuse hepatic fibrosis results.

HEPATIC LESIONS IN MAN ASSOCIATED WITH NOXIOUS AGENTS

Toxipathic Hepatitis in Man

Numerous examples of toxipathic hepatitis due to chemicals can be found in accounts of human cases of poisoning

A girl, aged 17 years, was anaesthetized with chloroform Next day she was drowsy, the day after jaundiced, and she died three days after the anaesthetic At autopsy the liver weighed 1800 g (normal 1500 g) and there was necrosis around the central veins of each lobule [106]

A child of 5½ years was given 1 c c of carbon tetrachloride and died forty-eight hours later The liver showed centrilobular necrosis involving half to two-thirds of each lobule [32, 80]

These are both examples of poisoning from substances which, in the usual dosage, are commonly without manifest ill-effects At first sight this low incidence of illness in human subjects might seem to suggest a discrepancy from the experimental work In animals, when these two chemicals are given under controlled constant conditions, pathological changes in the liver of approximately the same severity are consistently produced in all. But even in animals symptoms of liver damage, such as jaundice, are uncommon and the existence of such damage may easily be unsuspected if the animals are not killed to demonstrate its presence. Comparable 'subclinical human cases' have been noted [9] and, such hepatitis being a transient condition and liver damage in man being rarely suspected in the absence of jaundice, it is probable that many cases are overlooked. It is therefore likely that liver damage, after exposure to toxipathic agents, may be far commoner than is realized, and that the discrepancy between clinical and experimental observations may be more apparent than real

When more virulent poisons are taken, the incidence of fatalities is higher and the pathological lesions more extensive. At times the zonal necrosis may extend until it becomes massive, but usually traces of its primarily zonal character can be found on search When massive, however, it still differs from dietetic massive necrosis in being generalized and not partial in its distribution, and 'immediate', and not 'delayed', in its onset.

A man, aged 22 years, was admitted to hospital two hours after taking rat poison containing phosphorus Three days later jaundice developed and he died six days

pathic necrosis secondary to a toxipathic swelling of the hepatic parenchyma The terms relating to cellular pathology are, however, unsuitable for the broader conceptions of general usage. Inclusive terms comprehending the lesion as a whole are required. Of such the term hepatitis is most useful, for it can be applied, not only to the whole lesion, but also to the lesion in its different stages of development. The qualifications *toxipathic* and *trophopathic* can then be used in association with it to indicate the dominant factor in the causation of the particular condition. The lesions of the liver in infective hepatitis,

with exposure to noxious agents, it may be useful to summarize the broad characteristics of each kind of lesion.

Toxipathic hepatitis is characterized clinically by the shortness of *the latent period between exposure to the causative conditions and the* development of the illness. The usual pathological lesion is a zonal necrosis, uniformly distributed throughout the liver, but occasionally the noxious agent is so virulent, or present in such concentration, that the zonal necrosis extends to involve all the cells in the lobule *and becomes massive in character throughout the liver*

Trophopathic hepatitis, due to direct or indirect nutritional deficiency, has a delayed onset. It causes a massive hepatic necrosis which, even when it involves the whole organ, is usually at different stages of development in different places. Trophopathic hepatitis due to anoxia *is, however, of rapid onset, and leads to a zonal necrosis* which, on occasions, may extend to become massive.

Trophopathic hepatitis frequently occurs secondarily to those types of toxipathic hepatitis in which swelling of the hepatic parenchyma occurs. It is then due to this swelling impeding the intralobular circulation and so curtailing the supply of those factors essential to the life of the parenchymal cells. It is uncertain what part anoxia and what part deficiency of some essential nutriment plays in this necrosis. In

hepatic necrosis

The clinical and pathological sequelae in the survivors of these different types of hepatitis bear no relation to their cause. Massive necrosis, however produced, leads to post-necrotic scarring Zonal

and around the portal tracts, which not infrequently develops, is in all probability simply a response to the intralobular damage



FIG 44—Centrilobular necrosis in infective hepatitis From a fatal case in man (Lucké, B , *Amer J Path* , 1944, 20, 471)

(Fig. 9). All the [illegible]
infection with a [illegible]
the onset of sym[illegible]
period of incubati[illegible]
the onset of the symptoms of infection the liver becomes enlarged and tender. Many cases develop jaundice a day or two later, others subside[8, 20, 29, 31, 72, 82, 104] without doing so. In the ordinary case the symptoms of infection quickly subside, decrease in size of the liver follows, the jaundice fades, and before long the patient recovers completely Simultaneously, complete restitution of the liver to normal occurs.[54] Such cases have the features of a toxipathic hepatitis due to a single attack by a noxious agent; but in them the noxious agent is, not a chemical but the results of a virus infection

Not all cases of infective hepatitis, however, pursue this simple course. In some a massive necrosis supervenes This either kills the patient or leads to post-necrotic scarring The explanation of this [illegible]

after taking the poison At autopsy the liver weighed 1850 g and showed extreme fatty degeneration most marked at the periphery of the lobules[106]

A woman, of 26 years of age, ate thirty-five fungi which she believed to be mushrooms, but which were later found to be Amanita phalloides. She died four and a half days later The liver weighed 1 Kg and was yellow and friable On microscopic examination all the parenchymal cells showed fatty change or necrosis, save for occasional cuffs of healthy cells around some portal tracts[26]

After even a single attack of hepatitis from such virulent poisons as phosphorus,[78] or the toxin of Amanita phalloides,[27] the survivors may develop a fibrosis of the liver. The published data, however, are not sufficiently detailed to reveal its type. From analogy with animal experiments post-necrotic scarring would be expected

The above cases are all instances of poisoning by a single dose of a particular chemical. Repeated doses of poisons causing zonal necrosis lead, in experimental animals, to diffuse hepatic fibrosis The following examples illustrate the same effect in man.

[illegible]

[illegible] of chloroform would [illegible]

A similar fibrosis may also develop after long exposure to inorganic arsenic which is known to produce, though with difficulty, a centrilobular necrosis in animals.

A woman, aged 56, was admitted with signs of 'cirrhosis of the liver' and chronic arsenic poisoning For twenty years she had regularly taken full doses of liquor arsenicalis for psoriasis, but fourteen years before admission the treatment was discontinued She was a total abstainer, in good circumstances, and the W R. was negative At death a diffuse, hepatic, fibrosis was found

It is thus apparent that the clinical and pathological features, developing in man after exposure to certain chemicals, closely resemble those in experimental toxipathic hepatitis produced by the same poisons in animals / There are many illnesses, however, with the pathological features of a toxipathic hepatitis, in which there is no exposure to a chemical poison Infective hepatitis and homologous serum jaundice are examples.

It is now securely established that the pathological lesion in the acute stages of infective hepatitis and homologous serum jaundice is a zonal necrosis of the liver parenchyma.[1 25 35 59 84] Centrilobular necrosis is present (Fig. 44) and the cellular reaction in

The association between massive hepatic necrosis and infective hepatitis was first pointed out by Cockayne [17] in a masterly article published in 1912 and subsequent experience has amply confirmed his observation that the incidence of massive necrosis increases when infective hepatitis is epidemic.[7, 8, 11, 13, 15, 20, 33] The question thus arises as to whether the massive necrosis, which is seen with increasing frequency during an epidemic of infective hepatitis, is simply due to an accentuation of the infective process which usually produces a transient zonal necrosis; or is a separate and distinct condition which supervenes on the usually benign infective hepatitis? The former alternative may account for those cases dying within a few days of the appearance of illness [37, 35] and, as such, would be comparable to the massive hepatic necrosis seen after highly virulent poisons Such cases are, however, rare, and the majority would seem to have another explanation.

Cockayne drew attention to the many reports which indicated that pregnancy influenced the prognosis in infective hepatitis. Thus Ballot [4] recorded an epidemic in Martinique in which eight pregnant women were attacked Seven miscarried and all died with symptoms of ictère grave Bardinet had a similar experience in Limoges.[5] Cases are recorded of one member of a family developing, and then recovering, from mild infective hepatitis and later another member, who was pregnant, contracting jaundice and dying with massive hepatic necrosis [33] The reverse has also been noted; a pregnant woman dying of massive necrosis and, later, other members of the family developing infective hepatitis [41] The massive hepatic necrosis, which occurs in pregnancy in the absence of infective hepatitis, has already been mentioned, and it has been suggested that this may be a trophopathic lesion due to the diversion of essential nutriments from the mother to the foetus When infective hepatitis is also present the liability of the mother to develop such a complication would be considerably increased. That the massive hepatic necrosis seen in pregnant women is not due to any unusual virulence of the infecting agent is indicated by the observation that the livers of the infants born to such women are normal

If infective hepatitis is prevalent in famines and among malnourished persons, massive hepatic necrosis is also said to be relatively common. Unfortunately this opinion is not well documented. Before the first world war massive hepatic necrosis was a rarity in Central Europe During the war and for some years afterwards its frequency astonished experienced clinicians. In the opinion of the German physicians its increased incidence was related primarily to malnutrition and not

pondingly severe.[19] It has been observed on several occasions that outbreaks of jaundice in venereal disease clinics have coincided with the prevalence of infective hepatitis in the neighbourhood.[62 67 96 100] In the clinic patients, the incidence rate of jaundice was higher, and the mortality rate about ten times greater, than in the surrounding population with infective hepatitis.

Delayed Massive Hepatitis in Man after Exposure to Poisons

Following exposure to certain poisons illnesses develop, in a minority of the population at risk, which are characterized by the long latent period between exposure and the appearance of symptoms. At autopsy a massive hepatic necrosis, often most marked in the left lobes, is found.[94 102] The survivors develop typical post-necrotic scarring. Typical examples of such poisons are trinitrotoluene[22 50 73 74 99] and cinchophen.[38 53 83 89]

A boy, aged 16 years, was employed melting T N T from May 23rd to the end of June, 1916, when he was discharged and went to live on a farm. On August 28th he started to vomit, became jaundiced on September 1st, and died on September 9th At autopsy the liver weighed 550 g and showed changes typical of 'acute yellow atrophy'[106]

A woman, aged 54 years, on admission showed jaundice, oedema and vomiting Seven weeks previously her doctor prescribed cinchophen, and she had taken this substance in therapeutic amounts for five and a half weeks Jaundice developed ten days after taking the last dose On admission the case presented the clinical features of 'acute yellow atrophy' She died a month later and massive necrosis of the liver was found[45]

A woman, aged 30 years, was admitted with ascites ten years after an attack of jaundice which occurred when she was working with T N T At autopsy the liver was fibrosed and in places showed signs of subacute necrosis[106]

A woman, aged 46 years, had received courses of treatment with cincophen over three years She died in coma and with jaundice At autopsy post-necrotic scarring was found and the photograph of her liver shows atrophy of the left lobe[83]

These illnesses closely resemble that of dietetic massive necrosis and contrast conspicuously with those due to toxipathic hepatitis. *It is* suggested that they may be regarded as examples of a conditioned trophopathic hepatitis, developing in a manner similar to that suggested for experimental selenium poisoning.

Trophopathic Hepatitis as a complication of Toxipathic Hepatitis

In temperate climates massive hepatic necrosis usually occurs as a complication of a primary illness which ordinarily gives rise to a zonal necrosis and pursues the usual clinical course of a toxipathic hepatitis.

The association between massive hepatic necrosis and infective hepatitis was first pointed out by Cockayne[17] in a masterly article published in 1912 and subsequent experience has amply confirmed his observation that the incidence of massive necrosis increases when infective hepatitis is epidemic.[7, 8, 11, 15, 19, 20, 63] The question thus arises as to whether the massive necrosis, which is seen with increasing frequency during an epidemic of infective hepatitis, is simply due to an accentuation of the infective process which usually produces a transient zonal necrosis; or is a separate [illegible]

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[illegible] grave. Bardinet had a similar experience in Limoges.[5] Cases are recorded of one member of a family developing, and then recovering, from mild infective hepatitis and later another member, who was pregnant, contracting jaundice and dying with massive hepatic necrosis[39] The reverse has also b[illegible] massive necrosis and, later, [illegible] infective hepatitis[41] The [illegible] pregnancy in the absence of infective hepatitis, has already been mentioned, and it has been suggested that this may be a trophopathic lesion due to the diversion of essential nutriments from the mother to the foetus. When infective hepatitis is also present the liability of the mother to develop such a complication would be considerably increased. That the massive hepatic necrosis seen in pregnant women is not due to any unusual virulence of the infecting agent is indicated by the observation that the livers of the infants born to such women are normal.

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simply to the prevalence of infective hepatitis.[90, 98] Findlay[276] has recently published a most informative study of infective hepatitis in West Africa. The population at risk consisted of European troops, coloured troops and the local native population. Fatal cases died with massive hepatic necrosis. Although the incidence rate of the disease was two to four times as great in white as compared with coloured [illegible] times as great, [illegible] ites The dis- [illegible] Statistics for the mortality rate in the local native population were not available but a most suggestive epidemic was observed in the Cross River district. On the east bank of the river mortality was low, on the west bank high, reaching 30% in some villages Famine and malnutrition were rife on the west bank, on the east food was plentiful and nutrition relatively good In a study of yellow fever vaccine hepatitis the mortality rate from massive necrosis among well-fed American troops was 0·2%[29]; among ill-fed Brazilians it was 2·4%.[33] It is well established that, after injury, considerable amounts of protein are destroyed and lost to the body. In an epidemic of infective hepatitis occurring among wounded men the mortality rate from massive necrosis was 20%[109] as compared with 0·2% in unwounded subjects In this connection it is perhaps noteworthy that the mortality rate in patients developing homologous serum jaundice some months after an injury for which they required a transfusion is considerably higher than in cases of infective hepatitis.[120, 934] Finally Nixon[724] states *from his experience in Turkey that whether infective hepatitis in* pregnant women will or will not proceed to massive hepatic necrosis depends on the state of the mother's nutrition.

We have now considered massive hepatic necrosis arising under a variety of circumstances; in malnutrition, during pregnancy, after poisoning, and in association with infective illnesses. It is difficult to believe that such diverse conditions could lead to the production of a common toxin which, acting on the liver, would produce massive necrosis. But in each case there are indications of interference with nutrition; each produces conditions conducive to the development of a trophopathic hepatitis †

† My attention has recently been drawn to the remarkable, but little known, thesis by Mossé [illegible] which [illegible]

necrosis

The explanation of how an agent, which normally gives rise to a toxipathic hepatitis, can lead to the development of a trophopathic

necrosis, so that in extreme cases the whole lobule is involved and the lesion becomes massive in type. It is this type of massive necrosis which develops in man on the basis of a toxipathic lesion, and it is believed to arise in the following way.[45]

Human livers which are the seat of a toxipathic hepatitis are enlarged and swollen. That this indicates increased tension within Glisson's capsule can readily be seen at autopsy when, on slicing into the liver, the cut surface bulges over the capsules. In such cases the circulation within the liver must be impeded just as it is in the experimental animal under the same conditions (Fig. 19). The course of events in these cases depends upon three factors: the amount of essential nutriments circulating in the blood, the degree of circulatory restriction within the liver; and the duration of that restriction. The amount of essential nutriment, both in the blood and in the parenchyma, depends upon the presence, or absence, of dietary deficiency and such factors as anorexia, vomiting and pregnancy. If the amount of circulating nutriment is large then massive necrosis will not supervene and, the other variables being equal, the case will follow the course of an ordinary toxipathic hepatitis. If the amount is low then the zonal necrosis will extend and may even become massive in type.† If the amount is intermediate, massive necrosis will supervene only in those areas where the circulation is most impeded. But even in health the left vascular territory receives a lower concentration of essential nutriments than the right; and this discrepancy is necessarily exaggerated when swelling of the parenchymal cells throughout the organ impedes the circulation. The old observation[34 85 101] that massive hepatic necrosis, even when it supervenes on a toxipathic hepatitis, is often more marked in the left than in the right hepatic lobes[11 55 57 64 94 102] is thus explicable (Fig. 45). The degree of circulatory restriction within the liver is important because it determines the speed with which the parenchymal cells will be brought to a state

† Presumably the periportal cells, which are first exposed to the incoming portal blood and which have in consequence the best opportunity to obtain any available blood-borne nutriments, will necessarily be in a better state of nutrition than the more centrally placed cells. But as malnutrition increases in degree the zone of relatively well-nourished cells will shrink back on the portal tracts.

of deficiency. With complete arrest of the intralobular circulation their death is certain and rapid. With lesser degrees of restriction the

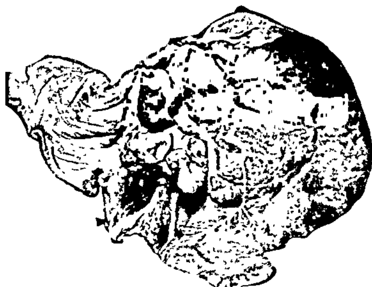


Fig 45—Atrophy of the left lobe of the liver From a fatal case of infective hepatitis (Lucké, B, *Amer J Path*, 1944, 20, 471)

development of massive necrosis will depend upon the other two variables, the amount of essential nutriments present, and the duration of the circulatory restriction.

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complication. But it is as well to be clear as to what can legitimately be expected from dietary therapy. Diet does not influence an uncomplicated toxipathic process and little benefit can be expected from giving supplements of protein, or of amino-acids, to well-nourished patients with such lesions. It need occasion no surprise, therefore, that dietary measures have been found to be largely ineffective in expediting the recovery of well-fed soldiers with infective hepatitis.[21 43 48 107] The one exception, however, is perhaps noteworthy. In the only trials in which supplements of cysteine were used a slight, but statistically significant, benefit was demonstrated.[79 108] What

might be expected, however, is that early, and intense, nutritional therapy might definitely benefit cases of toxipathic hepatitis when complicated by malnutrition Such a test has not yet been made. The administration of extra protein, or appropriate amino-acids, to cases of toxipathic hepatitis is thus to be regarded as a prophylactic measure against the development of a complicating, trophopathic hepatitis, and, as the supervention of this complication cannot be foreseen, it is a precautionary measure to be advised in all cases, but especially in those with a further condition, such as pregnancy, which may impair nutrition

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CHAPTER VI

THE SYNDROMES OF HEPATIC FAILURE

THE liver is a composite organ and this composite nature is preserved even in its smallest anatomical unit, the lobule. As a consequence injury to any part of it commonly involves several distinct, but contiguous, tissues. The symptomatology of a particular hepatic lesion may thus comprise several components, each due to disturbance of function in a different tissue; and as the lesion extends, the symptomatology may show a corresponding increase in complexity. But if symptomatology is to serve as a reliable guide to the nature of the underlying lesion it must be analysed into its component syndromes and the significance of each established. It is, therefore, of great importance to define those syndromes attributable to the functional impairment of each of the hepatic tissues, which, in combination, make up the clinical picture of hepatic failure.

The symptomatology of hepatic failure can be separated into three broad syndromes. Those of:

1. Excretory Failure.
2. Parenchymal Failure.
3. Portal Obstruction.

The first two are referable to failure of functions peculiar to the liver. The third, while not due to impairment of liver function, is frequently associated with such impairment because of the peculiar anatomy of the liver. Together with these three syndromes it is convenient to consider enlargements of the liver and the different types of hepatic pain.

THE SYNDROME OF EXCRETORY FAILURE

In the past such importance was attached to the accumulation of biliary constituents in the body that the ultimate clinical state of cases dying from liver failure was attributed to their toxic action and dignified with the name of cholaemia. Nowadays, however, its importance has been minimized. but it is still credited with the ability to produce, not only jaundice, but further ill-effects.

When the liver is prevented from excreting bile, the levels of phosphatase,[40, 48, 49] cholesterol,[23, 56] bile salts and bilirubin[1, 33] increase

in the blood. Of these, the first produces no symptoms, and the second only in those rare cases in which cholesterol is deposited in the skin, particularly in the creases of the palm, and gives rise to typical xanthomatous plaques. Retention of bile salts is said, but not proved, to account for the itching which is such a common feature in these conditions.[52] But the symptom *par excellence* of failure to excrete bile is jaundice.

As is well recognized, there are two broad clinical forms of jaundice; that due to failure to excrete bile and that due to excessive haemolysis. With the latter we are not concerned. Failure to excrete bile may occur either from obstruction in the large biliary passages or from inflammation of the liver. If the latter, then most of the organ must be involved, for it has been shown experimentally that 20% of the liver will suffice to remove all the bile pigment that is formed in the body under normal circumstances.[35,24]

There has, in the past, been considerable dispute as to the nature of the jaundice produced in conditions where there was no obstruction to the large bile ducts. It was known that many poisons which act on the liver parenchyma lead to jaundice, and that Weil's disease and yellow fever have a similar site of action. The jaundice of infective hepatitis was, formerly, regarded as the result of a catarrhal inflammation of the common bile duct and as the main example of an infectious process which produced extra-hepatic biliary obstruction. Now it has been shown that this condition is essentially a parenchymatous inflammation of the liver.[18,50] There is thus ample evidence that jaundice can, and commonly is, produced in conditions which primarily involve the liver parenchyma. At one time it was thought that this type of jaundice differed from that produced by obstruction to the larger bile passages, and it was differentiated from such obstructive jaundice by the term toxic jaundice.[18] The basis for this distinction was the van den Bergh test.[18,36,37,81] The plasma, in cases of obstructive jaundice, gives an immediate direct reaction with this test. Jaundice associated with inflammation of the liver, once called toxic jaundice, may give direct, delayed direct, or biphasic reactions. It is now believed that these latter variations do not indicate that the pigment in the blood differs in the two types of case,[24] but rather that the different types of reaction are the result of differences in quantity of the pigment present and of substances, such as cholesterol or bile salts, which modify the reaction.[3,29,67] It appears that the same bile pigment is retained in the blood whether the case be one of obstruction of the bile ducts or inflammation of the liver.

Examination of sections of the liver from patients with hepatic inflammation shows at once that the jaundice is not due to inflamma-

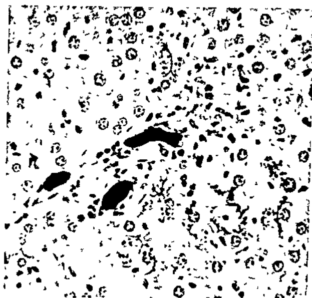


FIG 46—Biliary canaliculi Rat The bile ducts have been injected with Indian ink and the injection has passed into the minute biliary canaliculi which lie between the parenchymal cells and penetrate into their substance H and E × 320 (Reproduced by the courtesy of Dr L E Glynn)

tory obstruction of the small bile ducts. These are empty and normal in appearance and there are no signs of plugs of bile pigment in the ducts of the portal tracts. Bile pigment is, however, present in abnormal amounts in the central cells of the hepatic lobule, and not uncommonly the small intralobular biliary canaliculi are plugged with bile and some may even have ruptured[22] [1] These canaliculi are ordinarily no more than potential spaces between the parenchymal cells (Fig. 46).[1] Even slight swelling of such cells could hardly fail to obstruct such fine canals, and it would seem that the jaundice associated with inflammation of the hepatic parenchyma, be this due to a toxic or living agent, is produced in this way. The jaundice due to obstruction of the large bile ducts and the jaundice associated with inflammation of the liver thus seem to be essentially the same. Both are due to obstruction; but they differ in the nature and the site of that obstruction.

It is a clinical commonplace, however, that the symptomatology is very different in these two conditions. In inflammatory jaundice the patient is definitely ill from, or even before, the onset of jaundice; in jaundice from extra-hepatic obstruction the subjective feelings of illness are, at first, unobtrusive. There is one essential difference between these two conditions Inflammatory jaundice is complicated by extensive parenchymal damage; jaundice due to obstruction of the large bile passages, at least in its early stages, is not. If, therefore, the pure syndrome due to retention of biliary constituents is to be clarified, early cases of extrahepatic biliary obstruction should be studied

If one examines a series of patients with carcinoma of the head of the pancreas, one cannot fail to be struck by the contrast between their deep jaundice and their comparative sense of well-being. Some, indeed, are ill, but these are febrile and their livers show, on microscopic examination, an ascending cholangitis with inflammation of the periportal parenchyma. But excluding such complicated cases and confining one's attention to those in the early stages who are afebrile, then apart from the jaundice, and any symptoms arising from the condition causing the obstruction, they are essentially symptomless There is no apathy, malaise, anorexia, vomiting or somnolence Provided some bile is reaching the intestine to facilitate the digestion of food there is little significant loss of weight. Such patients are typified by one who, at a Christmas party, masqueraded with great success as a Chinaman. This is very different from the man with jaundice due to inflammation of the liver. He feels, at least, asthenic and, generally, ill. The contrast is the more striking when the levels of bile in the blood of patients with one or other of those conditions are compared Far higher levels are the rule in cases of extra-hepatic biliary obstruction. It is therefore evident that jaundice itself produces no major impairment of health. It is even doubtful whether such retention produces some of the minor symptoms which have been attributed to it. Traditionally, jaundice causes bradycardia. This conclusion would seem to be based upon a preferential attention to cases of infective hepatitis In mild cases with that condition, bradycardia often appears one or two days after the appearance of jaundice. It is not seen, however, in cases of jaundice due to extra-hepatic obstruction.

It thus appears that the only symptoms which can certainly be attributed to retention of biliary constituents in the body are jaundice, perhaps itching, and occasionally xanthomatous deposits in the skin;

and it is evident that such retention contributes little, if anything, to the grave general symptoms which occur in many conditions with jaundice.

PORTAL OBSTRUCTION

The frequent association of fibrosis of the liver with ascites and the development of a collateral circulation between the portal and systemic venous systems, has been known for a long time and interpreted as evidence that the fibrotic liver is obstructing the portal circulation. Perfusion of such livers has established that they do in fact offer obstruction to the inflow of portal blood [25] and direct measurements, during life, of the pressure within the portal vein of subjects suffering from hepatic fibrosis has demonstrated that portal hypertension is present in such cases.[5 58 59] To such hypertension the splenomegaly, the haematemeses, ascites and oedema of chronic hepatitis have been attributed, so th[illegible]
pres[illegible]
the [illegible]
circulation between the portal and systemic venous systems. There are *three sites where such may commonly be found during life*, at the junction of the oesophagus and stomach; where the rectum joins the anal canal; and at the umbilicus, where veins in the falciform ligament reach the surface and carry outflowing blood to the vessels in the abdominal wall. Of these, the first site is the one where such collaterals are most constantly found, and these are readily demonstrable by means of an opaque meal and radiography (Fig. 47). At the second site haemorrhoids are produced; but these are so common in all types of patient that their demonstration has no special significance in cases of hepatic fibrosis. Large veins issuing from the umbilicus and coursing over the abdomen are a classical but rare sign of portal obstruction In such veins the blood flows in the normal direction, upwards in the upper abdomen and downwards in the lower, and thus enables them to be distinguished from the venous collaterals, which develop after obstruction to the inferior vena cava, in which the flow is uniformly towards the head. An identical system of collateral veins develops in those rare cases which survive thrombosis of the portal vein in the absence of hepatic disease. Such vessels are, therefore, not evidence of liver disease but of portal obstruction. Their significance, in the [illegible]

chronic pathological processes in the liver, are invariably fibroses. Th fact that such evidence of portal obstruction may be discovered acci-



FIG 47—X-ray of the oesophagus while swallowing a thick preparation containing barium to show oesophageal varices From a case of 'Banti's syndrome

dentally is sufficient indication that, in itself, portal obstruction, provided that it is not complete, does not materially incapacitate

Ascites and Oedema

Oedema is a common feature in hepatic failure. In ambulant patients it commences round the ankles and rarely spreads beyond the

lower limbs. At one time it was explained as the result of ascites [illegible] veins and so obstructing the return [illegible] While this explanation may be valid [illegible] not account for the oedema which frequently appears weeks or months before fluid accumulates in the abdomen. Such oedema may temporarily disappear and so its occurrence be overlooked. But it occurs in the majority of patients with gradually failing hepatic function. It is correlated with a fall in the level of plasma albumin which, when such oedema is present, is usually below 3g /100 c.c. of plasma.[13,14] The fall in albumin may, however, be obscured by a concomitant rise of plasma globulin,[7,20,26,38,41,45] so that the total amount of protein in the plasma is at, or above, normal levels. Such an increase in globulin has no significant effect upon oedema formation. This pre-ascitic oedema in hepatic disease is probably, like other oedemas associated with low levels of plasma albumin, related to the reduced colloidal osmotic pressure of the plasma[11] The low levels of albumin in the plasma persisting after ascites has appeared, this factor is still present to reinforce any mechanical factors promoting oedema formation.

The same factors which determine the formation of oedema also influence the formation of ascites Three such factors are involved: pressure within the capillaries forcing fluid out of the vessels; the osmotic pressure of the plasma proteins drawing fluid back into the vessels; and the degree of capillary permeability. In addition two further factors may be concerned · removal of ascitic fluid by lymphatic drainage from the abdomen, and failure to excrete water and salt adequately in the presence of liver damage.[46]

Ascites is of common occurrence in chronic nephrosis and its appearance is correlated with the fall, and its disappearance with a rise, in the level of the plasma proteins. Hypoproteinaemia alone can thus cause ascites. But it is doubtful whether this factor by itself is ever responsible for the ascites of hepatic disease, although its important contributory rôle is undoubted.[32a] In nephrotic cases with ascites, gross and generalized oedema is always present In patients with lesions of the liver, oedema of this degree is absent, and its absence is presumptive evidence that the ascites in such cases is not entirely due to hypoproteinaemia.

[illegible] mitted [illegible] It is [illegible] llary pressure within the portal system in portal hypertension from hepatic

fibrosis. The experiments of Bolton[8,9,10] show that this factor by itself may cause ascites. He partially obstructed the inferior vena cava

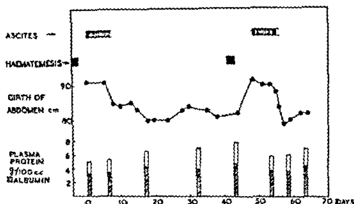


FIG 48—The relationship between ascites and plasma protein level The presence of ascites was judged by the sign of 'shifting dulness in the flanks' Data from a case of 'Banti's syndrome' with repeated haematemeses When the total plasma protein level fell below 6 g./100 c c., or the plasma albumin level fell below 4 g./100 c c., ascites appeared, only to disappear when the levels rose above these values These falls in plasma protein level were insufficient to produce oedema of the subcutaneous tissues Ascites did not appear until 24 to 48 hours after a haematemesis and, until this time, no fall in plasma protein level occurred

above the liver, thus producing portal hypertension. Within twenty-four hours abundant ascites formed which, however, gradually disappeared after two or three months, when a collateral venous circulation developed. Thrombosis of the portal vein in man, if not rapidly fatal, also causes ascites to develop Extreme portal obstruction alone can, therefore, produce ascites Whether the degree of portal obstruction found in cases of hepatic fibrosis is sufficient to do so is uncertain. Probably in the majority of cases the combined influence of portal hypertension and hypoproteinaemia are necessary This is illustrated in the above case shown in Figure 48, where a fall in the plasma protein level, insufficient to cause oedema, invariably led to the development of ascites In this case the degree of portal hypertension was apparently insufficient to cause ascites when the plasma protein level was normal, but sufficient to cause it when slight hypoproteinaemia was present

The colloidal osmotic tension within the capillaries depends upon the capillary walls preventing the passage of plasma proteins while allowing the free transit of water and electrolytes An increase in

capillary permeability, by allowing protein to escape into the ascitic fluid, would diminish the colloidal osmotic pressure difference across the capillary wall and so seriously impair the mechanism for drawing such fluid back into the circulation[19, 31, 34] The majority of investigators have found that the protein content of different ascitic fluids ranged from 0·1 g./100 c.c. to 2·0 g./100 c.c.;[41] but values as high as 3·8 g./100 c.c. have been recorded.[12] Values of the order of 0·1 g./100 c.c. indicate that in those cases the fluid was a simple transudate formed through a capillary wall with normal permeability, the higher values, in the other cases, that permeability was increased That such increased permeability is confined to the abdomen is shown by the observation that the permeability of the systemic capillaries in cases of hepatic fibrosis is normal.[54] How such increased permeability comes about is unknown.[46] Inflammation *from infection* plays a part in some cases, but the character of the cells in the ascitic fluid do not suggest its presence in many. It may be that, just as congestion in the systemic system leads to anoxia of the capillary wall and so increases its permeability,[33] so congestion in the portal *system influences the permeability of the portal capillaries*

Obstruction to the abdominal lymphatic drainage may lead to an [illegible] milky appearance of the ascitic [illegible] In the ascites of hepatic fibrosis [illegible] But this milkiness is not usually due to fat, for shaking with ether will not remove it. It is caused by the presence of a lipo-globulin complex.[60] As a similar substance occurs in the ascites of cases with nephrosis, which is entirely related to hypoproteinaemia, its presence would not seem to indicate a fault in the lymphatic drainage of the abdomen. Little is known about the function of the abdominal lymphatics in removing fluid from the abdomen once ascites is formed, but the absence of fat in the ascitic fluid from cases of hepatic fibrosis suggests that obstruction to the lymphatic drainage is not a factor in its production.

Recently evidence has been produced that a factor with a more general action, retention of fluid within the body, may contribute to the formation of ascites. Seventy years ago Mossé[104] described the oliguria which marks the onset, and the polyuria which signals the recovery from, acute hepatitis, and clearly established its prognostic significance His work seems to have been largely overlooked, but several observers have made the observation since.[144, 294] Ralli and her

collaborators have now shown that the urine of cases of liver disease with ascites contains considerable amounts of an antidiuretic principle; that this diminishes in quantity when ascites ceased to reaccumulate, and that the substance is not present in excessive amounts in the urine of patients with liver disease who have never had ascites.[46] This antidiuretic principle closely resembles pitressin in its pharmacological properties and the possibility is raised that, in liver disease, the ability of the damaged organ to destroy this substance is impaired so that fluid is retained in abnormal amounts to contribute to the formation of ascites and oedema

Ascites may thus be the resultant of several factors, the degree of influence of each varying in different cases. All these factors—diminution in the colloidal osmotic pressure of the plasma, increased pressure within the capillaries, fluid retention, and defective lymphatic drainage—are factors which influence fluid interchange anywhere within the body and if generalized would produce not only ascites but oedema. But it is evident that the salient feature of the ascites of liver disease is accumulation of fluid in the peritoneal cavity *without* the occurrence of gross generalized oedema. Any explanation of its mechanism must account for this localization Of the factors which may be involved in such a localization three are orientated to the abdomen—portal hypertension, local increase in capillary permeability, and defective drainage by the abdominal lymphatics. That the latter factor is concerned in any, save true chylous ascites, is at present a mere theoretical possibility Reasons have been given for thinking that, in the absence of peritonitis, increased permeability of the capillaries in the portal circulation may be simply a secondary result of portal congestion Portal hypertension is thus left as the single most important localizing factor. As we have seen, however, its influence is often facilitated by the simultaneous presence of hypoproteinaemia and to the combined influence of these two factors the occurrence of ascites may be primarily attributed in the majority of cases. Obviously, however, the condition of ascites implies the retention of fluid within the body and any factor tending to increase such retention, such as an [illegible]

when hypoproteinaemia was only moderate; little fluid retention but slight ascites even though the plasma protein level was unequivocally low

If such be the underlying mechanism it might be expected that ascites would always develop gradually. Experience shows that often it appears with remarkable suddenness. In some such cases portal thrombosis has occurred but, in most, the portal vessels are normally patent. It seems, in these latter cases, as if some critical value in the interplay of forces which normally prevent ascites had been passed. A slow fall in the plasma protein value would be without effect until it sank below the level required to balance the portal hypertension. Then ascites would appear relatively quickly. In others, the sudden onset of ascites coincides with an exacerbation of the hepatic lesion and the parenchymal swelling, consequent upon this, may well increase still further the obstruction to the blood-flow through the liver and raise the portal pressure to still higher levels. In yet others a sudden failure of parenchymal function may result in a rapid accumulation of the anti-diuretic factor, with consequent fluid retention, which would aggravate

the ascites of severe cases of acute hepatitis.[19] Certain cases in the course of an epidemic of infective hepatitis may become severely ill and ascites appears within a few days or weeks of the illness developing. Some recover. Others die, and at autopsy massive necrosis of the liver is found.[6, 17] Such cases do not usually show massive oedema and the ascites is, therefore, presumably not entirely due to hypoproteinaemia. It might be due to portal hypertension consequent upon the swollen liver obstructing the portal blood-flow, with, and perhaps in addition, a failure to destroy the anti-diuretic factor.

The significance of the phenomena due to portal obstruction can be summarized in a few words.

Portal obstruction alone, provided that it is not complete, does not cause ill-health and only incidentally threatens life by leading to the development of collateral veins which may rupture and cause a fatal

decreased Neither ascites nor portal obstruction, in themselves, materially contribute to the fatal outcome in the liver disease.

ENLARGEMENT OF THE LIVER

Enlargement of the liver may occur for six different reasons:

1. Engorgement with blood.
2. Engorgement with bile.
3. Inflammation.
4. Hyperplasia
5. Infiltration.
6. New growths.

In each case the enlargement is associated with some increase in consistency and this, together with the demonstration that the upper border of the organ is in its normal place, serves to distinguish enlarged livers from those which have either fallen or been displaced downwards.

Uncomplicated engorgement with blood or with bile, due respectively to obstruction of the venous or the biliary outflow, causes a uniform enlargement of the organ without distortion of its natural shape. [illegible]

congestion

Inflammation may be either local or diffuse. If strictly localized, as in a gumma, the signs are those of a local tumour. If diffuse the liver is generally enlarged and, in the early stages of inflammation, the enlargement presents the same features as in engorgement. The dis- [illegible]

of exposure to a condition which gives rise to hepatic inflammation. Focal inflammatory lesions in the liver, if sparse, cause no change in the organ, if numerous, the inflammatory reaction round them is sufficiently marked to produce the symptoms and signs of diffuse inflammation. Inflammatory enlargement of the liver is to be attributed partly to the infiltration by inflammatory exudation, partly to an intrinsic oedema of the whole parenchyma [28]

Chronic inflammation of the liver causes changes in shape and an increase in consistency approaching hardness. The hardness depends largely upon the amount of fibrous tissue present. Hyperplastic nodules are often present and these, though composed of parenchyma,

are themselves firmer than normal liver tissue owing to their tightly distending the fibrous tissue capsule which circumscribes them. The distortion in shape depends upon the degree or uniformity of the process throughout the organ. In diffuse hepatic fibrosis the general shape of the organ is preserved, but it is hard to the touch, and the edge has a granular roughness and is blunter than normal. Such livers, after an initial enlargement, may shrink and become smaller than normal. Portal obstruction is frequently associated with them. But when the inflammatory process is more irregularly distributed, as after massive hepatic necrosis, distortion may be marked. This is evident on palpation of the liver edge, which is coarsely nodular and may approximate to the spleen in thickness. Frequently such lesions affect the left more than the right lobes, and the hyperplastic nodules may then be more marked on that side. In such cases, clinical examination discloses an apparent enlargement of the left lobes, so that the lower border of the liver appears to run more horizontally than normal across the abdomen. Portal obstruction is a relatively late development in such lesions, but splenomegaly is usually conspicuous. The irregular enlargements of the liver are often difficult to differentiate from similar enlargements due to carcinoma A history of the symptoms of parenchymal damage for months before discovery of the hepatic changes, the relatively slow alterations in size of the organ, and splenomegaly, if present, are points in favour of the diagnosis of chronic inflammation

Infiltrations of the liver are of two kinds: diffuse and local. Diffuse infiltrations of the liver produce physical signs in the organ similar to those of engorgement or acute inflammation, and can be distinguished only on the basis of collateral evidence. Local infiltrations, as from secondary deposits of carcinoma, produce hard localized nodules which distort the liver shape. Such lesions can be suspected when hard nodules are found embedded in a liver of otherwise normal consistency. But if the deposits are numerous. the whole organ feels hard and irregular In either case the absence of symptoms of parenchymal damage, preceding by months or weeks the detection of the enlarged liver, should raise a strong suspicion of the nature of the condition.

HEPATIC PAIN

Two main types of pain can be clearly distinguished as arising from the liver. The first is due to inflammation of the peritoneum, the second to distension of the organ.

Peritoneal hepatic pain is either present only on respiratory movement or, if continuous, is exacerbated by such movements. In mild cases it is often confused with pleuritic pain being present only as a sharp stab on laughing or deep inspiration. It is usually felt in the side over the right lower ribs, but it may be referred to the tip of the right shoulder or suprascapular region; more rarely to the region of the inferior angle of the right scapula or the epigastrium. When continuous it is referred within the same territories. If the liver is enlarged, sharp pain may be produced by pressure, as from a belt, especially during inspiration. Such peritoneal pain is associated with pyogenic inflammations in the liver. It is therefore frequently found in cases of cholangitis and rarely seen in inflammatory conditions confined to the parenchyma. Occasionally it occurs in association with carcinoma in the liver, and in such cases examination of the liver usually discloses that the peritoneum is involved.

When the liver enlarges rapidly, then the patient becomes conscious of discomfort in the upper abdomen. In mild cases this discomfort is only produced under certain circumstances, in others, it is present as a dull sensation which can be exacerbated to pain, in the most severe the pain may be so intense as to suggest an acute abdominal emergency. It is often associated with vomiting. On examination tenderness is always present over the liver, and that this arises from that organ is shown by the sharp burst of the pain produced when the liver edge is sprung under the fingers. This pain is roughly localized over the part of the organ palpated. Thus palpation in the loin causes pain in that region and not in the epigastrium. In mild cases the patient's complaint is often of 'indigestion'. He reaches this conclusion because the pain tends to occur after meals and is felt in the epigastrium. But observant patients may notice that the pain is brought on by bending forwards, is relieved by lying supine, and occurs after large but not small meals. It appears that the 'indigestion' is due to a distended stomach pressing on a liver unduly sensitive to pressure. In such cases a blow over the right ribs will provoke typical pain in the epigastrium presumably by driving the left lobes of the liver against the structures in the left side of the upper abdomen. This mild type of distension pain is well seen in the early stages of infective hepatitis. Then it is usually interpreted as evidence of 'gastritis', although gastroscopy shows that the gastric mucosa is normal.[2] It occurs in its most severe form in some cases of diabetes, who are passing into coma, and whose livers are being rapidly distended by accumulation of fat. In such cases it tends to be felt over the right ribs as well as in the epigastrium. This condition has been

termed the 'diabetic acute abdomen'. In intermediate degrees it occurs in congestive cardiac failure and when carcinomatous deposits are rapidly growing in the liver. It is not so common in children, and in this connection it is noteworthy that, in such conditions as the acute hepatomegaly of diabetic coma, the liver in children is larger and softer than in adults, and usually not tender. Presumably in the young the liver capsule is more capable of distension. The severity of the distension pain is proportional to the speed of hepatic enlargement. It does not arise from livers, however large, which takes months to develop. The significance of the pain is, therefore, that it indicates an acute process in the liver.

A possible variant of thi[illegible]
[illegible]
abdomen may be noticed in the [illegible]
[illegible]
pain consequent upon the cholangitis.

A further pain, which occasionally occurs in patients with an enlarged liver, is situated in the epigastrium and over the left lower ribs and may spread round towards the back of the left chest. Its duration is measured in minutes, but it may be very unpleasant while it lasts. Its explanation is obscure

These are the pains which may arise in association with hepatic enlargements In practice they must be distinguished from pains arising in the gall bladder or larger biliary passages.

THE SYNDROMES OF PARENCHYMAL FAILURE

The syndromes due to failure of biliary excretion, portal obstruction
[illegible]
of all body tissues depends in v[illegible]
parenchymal damage has wide[illegible]
The disorders of intra-cellular[illegible]
result from impairment of function in the hepatic parenchyma, are

not yet elucidated The evidence that they occur rests upon the clinical observations that in hepatic disease, disorders develop also in other tissues.

Patients with active parenchymal disease are aware that they are not well. In mild cases this amounts to little more than an impaired capacity for mental or physical effort, together with some loss of weight and a lack of interest in, or disinclination for, food. Such symptoms occur in many diseases, but when they develop in the presence of signs of a hepatic lesion, they suggest that the parenchyma is involved These symptoms, in greater or less degree, are a feature of parenchymal failure in all its stages Other symptoms, however, only appear at particular stages. For convenience of discussion, therefore, such failures will be divided into acute, chronic and extreme forms. It should be realized, however, that the acute symptoms may merge into the chronic and that the extreme symptoms may supervene on either.

Acute Parenchymal Failure

In acute, diffuse, inflammation of the parenchyma of moderate severity, the patient is conscious of malaise, asthenia, nausea and anorexia Typically he is apathetic, spends most of the day drowsing, but often, at night, his sleep is disturbed by unpleasant dreams. The explanation of these symptoms is unknown, the only point which has been established being that, while anorexia persists the patient has a histamine resistant achlorhydria [27] In very mild cases the symptoms are of short duration, icterus may not develop, and the patient continues at work. In more severe cases he takes to bed and jaundice appears in a few days In severe cases extreme symptoms may rapidly supervene and the majority of such patients die A peculiar foetor is often present in the breath and this can only be compared to the smell of a freshly opened corpse Pathological investigations reveal, in addition to failure of biliary excretion, evidence of parenchymal injury Tests indicative of actively occurring damage, such as the cephalin-cholesterol flocculation test, are positive,[38] tests of liver function, such as the hippuric acid test, indicate impairment, and a slight fall in the plasma albumin level may develop [24, 46]

Chronic Parenchymal Failure

The first definite clinical sign that chronic progressive parenchymal failure is established is the appearance of oedema of the ankles. This is found to be associated with a fall in plasma albumin. In the absence

of starvation or gross albuminuria, such a fall in the plasma albumin level discloses serious impairment of a synthetic function of the parenchyma.[21, 41] If there is a concomitant elevation of the plasma globulin, then a subnormal level of plasma albumin has been present for a considerable time. Experience shows that these findings in the presence of a chronic liver lesion, such as a persistently enlarged liver, indicate that the liver damage has reached an incurable stage and, often, entered on a swiftly progressive course. At this stage other signs develop sooner or later.

Pulsating spider angiomata are commonly present on the skin, particularly over the forehead, hands and forearms. But these are not diagnostic of liver disease.[4, 42, 61] They also appear in some normal people and during pregnancy, but their recent development in patients with hepatic disease is suggestive of serious parenchymal failure. It is possible that one traditional symptom of hepatic fibrosis, epistaxis, is related to the development of similar angiomata in the nasal mucosa.[42] Associated with these there is often a mottled flushing of the palms and soles, together with sweating, which may be so profuse as visibly to exude on the patient's skin. These signs are not persistent, but over periods of weeks may wax and wane Bean[4] has produced evidence that their development and persistence is related to an excess of oestrin-like compounds in the body. He attributes their appearance in liver disease to that organ being so damaged as to be unable to destroy such compounds. The testicular atrophy[154] and gynaecomastia sometimes observed in chronic failure may have the same cause.

Anaemia is common in chronic parenchymal failure.[63] Two types may occur. The microcytic, or normocytic hypochromic variety, has no peculiar features, is of no prognostic significance, and usually reacts slowly to iron. It may be explained in some, but not all, cases as an iron-deficiency disease consequent upon impaired appetite. The second type superficially resembles pernicious anaemia in showing an increased mean cell diameter and colour index. The haematocrit value is, however, low so that the cells in this anaemia must be abnormally broad and thin. Examination of the bone marrow shows numerous macronormoblasts but no typical Ehrlich's megaloblasts. Further, the liver in such cases contains ample stores of the haemopoietic factor.[53] This anaemia is similar to that produced experimentally by deficiency of methionine,[24] but it does not react to an excess of dietary protein, liver extracts or iron. While not diagnostic of parenchymal failure, the development of such an anaemia, in a

patient with chronic liver disease, suggests that parenchymal function is now seriously impaired.

In the absence of fever the level of leucocytes in the circulating blood is either unchanged or decreased.[51] Leucopenia is particularly apt to occur in those cases with conspicuous splenomegaly;[47] and this point is of importance in relation to the pathogenesis of Banti's syndrome.

Some patients with chronic parenchymal damage show signs of deficiency of vitamin A or K, and this despite their consuming a normal diet. Vitamin A deficiency manifests itself in these cases as a folliculosis, or even a follicular hyperkeratosis, which is cured by giving preformed vitamin A but not by carotene.[47] Vitamin K deficiency in hepatic cases may cause excessive bleeding from cuts or even spontaneous ecchymoses under the skin. The nature of these haemorrhagic phenomena is shown by the low level of prothrombin in the blood.[55] This deficiency may occur under two conditions. When bile cannot reach the gut, vitamin K is not absorbed and a deficiency state then develops. In such cases intramuscular injection of the vitamin restores the prothrombin level to normal in a few hours. But it may also develop in patients with liver disease in whom ample amounts of bile are reaching the gut and, in these, injection of vitamin K is without effect on the low prothrombin level in the blood.[43, 62] In such cases parenchymal failure is so far advanced that the injected vitamin cannot be utilized.

Throughout this stage the general signs persist and their severity is a useful indication of the extent of the parenchymal failure. The less severe cases can, with effort, support their normal life, interpreting their inertia as 'neurasthenia' and disregarding the persistence with which their weight remains subnormal.

Extreme Parenchymal Failure

Several of the manifestations of chronic failure require time to develop, and when extreme parenchymal failure develops in an acute illness these are nc [illegible]
angiomata, the '[illegible]
tioned vitamin [illegible]
with extreme failure a fall of plasma albumin may occur, and be sufficiently severe to cause slight oedema, but there is not time for the development of that increase in plasma globulin, which in chronic cases accompanies such a fall.

Clinically, the patient in extreme failure shows the general symptoms to a conspicuous degree. Weakness is marked, appetite absent, vomit-

ing frequent. Bleeding into the skin and from the mucous membranes may occur. Particularly ominous are mental changes. Clouded consciousness interrupted by hallucinations are most common but delirium amounting to mania may occur. Occasionally a euphoria, in conspicuous contrast to the gravity of the patient's condition, develops. The characteristic foetor hepaticus is marked. The pulse rate rises steadily but, unless the patient was previously febrile, the temperature is not elevated until near the end, although the skin is often flushed and drenching sweats may occur. The patient becomes incontinent and slowly lapses into coma. This coma is peculiar in possessing no striking features. The patient seems quietly asleep and his condition is only revealed when attempts to rouse him fail. It is then often found that his limbs have a peculiar 'clasp knife' rigidity, not unlike that in Parkinson's syndrome, ankle clonus is present, and the plantar responses are extensor.[164] Occasionally fine tremors and spasmodic movements are present; rarely convulsive attacks occur. In this stupor he may remain for days, the circulation remaining good and the extremities warm. The majority quietly die, but dramatic recoveries may occur with sudden and perfect return of consciousness. In fatal cases a mildly acidotic type of breathing develops towards the end.

Little is known regarding the explanation of most of these symptoms. The haemorrhages in some cases are related to prothrombin deficiency, in others to lack of fibrinogen, both of which findings disclose extreme failure of parenchymal function. The rare convulsive attacks may sometimes be due to hypoglycaemia consequent upon impairment of the glycogenic function of the liver. The peculiar rigidity of the limbs is, like other similar syndromes, associated with degenerative changes in the basal ganglia.

Chemical examination of the body fluids in such cases reveals further evidence of failure of the hepatic parenchyma. In the absence of dehydration, or weakening circulation, the failure to synthesize urea from ammonia is shown by the falling blood urea and the rising urinary

of acute liver atrophy was first demonstrated by Frerichs.[22] But they are a rare finding. By modern chemical techniques, however, excessive amounts of many amino-acids can easily be demonstrated in such urines. The most convenient technique is by means of chromatography,[15] which allows daily estimations of their excretion. The presence of excessive amounts, particularly when these are increasing,

is of ominous import. Such amino-aciduria has been attributed to autolysis of dead liver tissue in vivo. This explanation appears to be only partially correct. In experimental animals the degree of hepatic necrosis can be varied by altering the dose and method of administering the poison Autolysis of liver cells occurs in all cases, but amino-acidura does not develop if any considerable portion of healthy parenchyma remains It seems that healthy parenchyma can metabolise the amino-acids liberated by autolysis In that case amino-aciduria signifies, not only that liver cells have been killed, but also that few survive.

Of similarly grave significance is a marked fall in the cholinesterase content of the red blood cells. The plasma cholinesterase level falls in any case of hepatitis, but that in the red cells only when the condition is desperate[604]

To illustrate the features in terminal liver failure, the following case of acute massive hepatic necrosis after cinchophen poisoning is described.

The patient was a woman, aged 54 years, who had suffered from swelling of the small joints of the hands and feet for ten years Between the 2nd May, 1941 and the 15th June she received 22 5 g of cinchophen, but then feeling vaguely ill she stopped taking the drug A week later she began to vomit, her urine became dark, her stools pale and three days afterwards jaundice was noted

On examination the patient was deeply jaundiced and drowsy She replied intelligently to questions, but volunteered no information She was not depressed, did not complain of feeling ill, showed no anxiety and watched her examination in a detached way and with a slow smile The temperature and pulse rate were normal The breath had the sweet smell of foetor hepaticus The liver was palpable three fingers' breadth below the right costal margin and the upper border of liver dulness was at the 6th intercostal space The spleen was not palpable The test of shifting dulness indicated a slight amount of ascites in the abdomen The urine contained bile, a trace of albumin, and tyrosine, but not leucine, crystals The stools contained bile

[illegible]

stage oedema of the legs and back began to appear, and the plasma protein level was found to have fallen to 5 8 g /100 c c. The liver was no longer palpable A fortnight after admission purpuric areas appeared on the arms and the occult blood test became

positive in the stools She was now quietly stuperose but showed occasional twitching of the arms The pulse rate and temperature then began to rise, reaching 120 and 101° F. respectively. She died quietly twenty days after admission, six weeks after the onset of jaundice

At autopsy the liver weighed 1080 g It was shrunken, flabby, friable and orange yellow in colour The bile passages and the spleen were normal. The peritoneal cavity contained dark-brown fluid Microscopic examination of the liver showed the later changes of acute massive necrosis

LIVER FUNCTION TESTS

The syndromes resulting from failure of the different systems of the liver have now been outlined. It is convenient, therefore, to consider the general value and broad significance of liver function tests[38, 614] Their use can be viewed from two aspects. They can be regarded as a means of demonstrating the absence of liver damage, or as a means of [illegible]

damage.

The presence of jaundice is a sufficient indication of the inability of the liver to excrete, and tests of excretory function are useful only as an index of progress or for establishing that the liver has recovered from such inability. Of these the brom-sulphthalein test is perhaps the most useful.

Similarly a persistently low level of plasma albumin in a patient, who has had signs of liver disease, is a sufficient proof of the failure of one synthetic function of the parenchyma, provided that the food intake is adequate and gross albuminuria absent Of similar, but perhaps more significant, import is a persistent depression of the plasma cholinesterase level.[604] In the absence of this finding the hippuric acid synthesis test may be useful for a normal result practically excludes impairment of parenchymal function.

[illegible]

For many years now clinical-pathologists have sought for a reliable test to differentiate extra-hepatic obstruction from inflammatory jaundice. None devised has proved entirely certain; and it is difficult to see how one could be. Cholangitis and consequent parenchymal damage sooner or later supervene in the majority of cases with obstruc-

tion to the bile ducts. It is only in the earlier stages that negative reactions to the empirical tests for liver damage, or normal responses to the tests for synthetic power, can be expected. Later [illegible] correctly, indicate that the hep[illegible] It seem[illegible] con[illegible] But [illegible] cases, in atte[illegible] types of jaundice. There is yet no test [illegible] approaches in value a careful clinical assessment of the patient and none which can be interpreted without it.

PUNCTURE BIOPSY OF THE LIVER

A consideration of the sequence of events following each of the different types of experimental liver injury has shown the importance of appreciating the anatomical form of the lesion in order to foresee the future course of events. Therein lies the value of puncture biopsy of the liver. But the procedure is not without its danger and its limitations. Its main danger is haemorrhage from the perforation in the liver, and puncture biopsy should never be done on any patient who is either bleeding or whose prothrombin index is subnormal. Failure to secure a specimen usually occurs when the organ is fibrotic and further, in such cases even when a specimen is secured, it may be misleading for the small sample may be unrepresentative or consist solely of parenchyma which has been sucked off the fibrous stroma. Within these limitations puncture biopsy is valuable for, often, it is only by its use that a precise diagnosis can be made and, when diagnosis is doubtful, treatment, advice and prognosis are apt to be hesitant and perhaps, in consequence, the handling of the patient ineffective.

But it is still a matter of controversy whether in view of its slight but undeniable risk the procedure is justifiable in clinical practice. Taking an overall view—which is the only attitude one can take towards a diagnostic procedure—the advantages of its discriminative use seem to outweigh its dangers. One of the most important differential diagnoses in the field of liver disease is between parenchymatous hepatitis and obstructive jaundice. Operation may be imperative and urgent in the latter but hazardous in the former. By means of puncture biopsy the differentiation can often be made. Owing to the great functional reserves of the liver apparent clinical recovery from infective hepatitis may have occurred at a time when the organ is still the seat of pathological changes. Experience has shown that a careless regime of life may

lead to an exacerbation of acute illness in such cases. It is difficult to convey to a patient, imbued with the sense of returning well being, the conviction that continued precautions are still necessary unless the doctor himself is inspired by the certainty of his diagnosis. In fibrotic conditions of the liver an exact diagnosis can be a decisive factor in prolonging the patient's life. Little can be done for cases of post-necrotic scarring, but much for the diffuse hepatic fibroses following fatty infiltration. The discovery of fat-laden parenchymal cells in a liver, diffusely fibrotic to a great or less degree, is an indication that the liver cells are malnourished and in urgent need of substances which can be supplied by appropriate dietetic therapy. The majority of such cases in temperate climates are alcoholics, who are notoriously unsatisfactory patients. Their survival may often depend upon the insistence with which they are pressed to reform their vicious habits and adhere to an appropriate dietary. The seriousness of such cases is often not clinically obvious until their last stages. Puncture biopsy by allowing its appreciation at an earlier stage may enable a decisive influence to be brought to bear on many members of this group while their illness is still curable. These are all practical considerations directly related to the patient's welfare in particular cases. Its wider practical value depends upon the importance attached, in any case, to knowing the exact diagnosis, and therefore the prognosis, as accurately as possible.

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CHAPTER VI

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CHAPTER VII

THE CLINICAL CLASSIFICATION OF LIVER DISEASE

Classification of disease is essentially a practical measure which aims at grouping together the related conditions from a mass of data so as to facilitate the understanding of the whole. The criterion of its adequacy is pragmatic. In respect of those diseases, all of whose manifestations are due to the continued operation of one cause, the ideal classification is based on aetiology; and such a classification has been applied with success to the specific infectious fevers. But it is doubtful whether an aetiological classification would be desirable, even if possible, for diseases which predominantly involve one organ. In these, although a single agent may be responsible for initiating the process, the course of the disease is determined, not by its continued operation, but by the inevitable consequences of the particular pathological change it initiates in the organ. These considerations are particularly relevant to the classification of hepatic disease. In that organ the same pathological changes may result from many different agents, some toxipathic and some trophopathic, but it is to the nature and extent of these pathological changes, rather than to the agent which initiates them, that the clinical manifestations, course and prognosis in the particular illness are related. In the present state of our know- [illegible] disease must largely [illegible] say, however, that [illegible] cluded In the early stages of many hepatic diseases, the symptoms and signs referable to liver damage are associated with general or local effects, which indicate the nature of the causative agent operating in the particular illness, and so provide data for their more complete understanding and management But in any particular case, acute or chronic, the immediate and remote assessments of the hepatic illness are based on other considerations: the immediate, on the degree of functional failure in the [illegible]

[illegible] in the subsequent chapters.

CLASSIFICATION OF DISEASES OF THE LIVER

1. INFILTRATIONS.
   - (a) Intrinsic.
   - (b) Extrinsic.
2. PARENCHYMATOUS HEPATITIS.
   - (a) Acute.
     - i. zonal.
     - ii. massive.
   - (b) Subacute. massive.
   - (c) Chronic.
     - i. post-necrotic scarring (chronic massive hepatitis).
     - ii. diffuse hepatic fibrosis — after recurrent zonal necrosis — after chronic infiltration.
3. BILIARY LESIONS.
   - (a) Obstruction.
   - (b) Cholangio-hepatitis.
4. CIRCULATORY LESIONS.
   - (a) Absolute ischaemia.
   - (b) Relative ischaemia.
5. FOCAL LESIONS.
   - (a) Inflammatory.
   - (b) Cysts.
6. NEW GROWTHS.
   - (a) Primary.
   - (b) Secondary.

CHAPTER VIII

INFILTRATIONS OF THE LIVER AND POST-INFILTRATIVE FIBROSIS

Infiltrations

1. *Acute and Subacute.*
   (*a*) Intrinsic —Fatty.
   —Glycogen.
   (*b*) Extrinsic—Lipoidoses.
   —Reticuloses.
   —Amyloid.
2. *Chronic.*
   Post-infiltrative fibrosis (Diffuse hepatic fibrosis)

The infiltrations of the liver may be divided into two groups according as to whether the infiltrating material is formed *in situ* or reaches the liver from outside. The former may be termed 'Intrinsic Infiltrations', the latter 'Extrinsic Infiltrations.' In the intrinsic infiltrations, the infiltrating material is confined to the parenchymal cells where presumably it is formed. They are to be regarded as exaggerations of some normal parenchymal function. The extrinsic infiltrations, on the other hand, primarily involve tissues which the liver has in common with other organs. With the exception of amyloid disease, which affects the blood vessels, this group of infiltrations involve the reticulo-endothelial system although, in advanced cases, the infiltrating material within the liver may not be limited to the Kupfer cells but spread also to the contiguous parenchyma The hepatic involvement in extrinsic infiltrations is essentially but part of a generalized condition.

Clinically, this group of conditions is characterized by a symptomless enlargement of the liver. Their onset is insidious, their course prolonged, they do not cause jaundice, they never lead to hepatic failure, and but for the fact that an enlarged liver were found in the routine examination, the existence of an hepatic lesion would not be suspected Splenomegaly, as might be expected from their pathology, is a feature in extrinsic, but it is absent in intrinsic infiltrations. Diffuse hepatic fibrosis, in various degrees, has been observed to develop in all infiltrations save those due to a primary disease of the reticulo-endothelial

system Its absence from this group is to be attributed to their course being measured in weeks or months rather than in years

The enlargement of the liver has the same features in all. It affects the whole organ uniformly so that the shape is not distorted The liver edge extends obliquely upwards across the abdomen from right to left It is smooth and straight save where it is interrupted by the falciform notch In consistency the organ varies from firm to hard according to the degree of fibrosis. Pain and tenderness are only found when the enlargement has been rapid, as in the fatty infiltration preceding diabetic coma or in an unusually swiftly progressive reticulosis But the most characteristic clinical feature is the thinness of the liver edge on palpation In other uniform enlargements of the liver the edge is blunted or thickened, in the infiltrations it is a sharp, firm, border, unless fibrosis is supervening, when it may take on the characteristics of the liver edge in diffuse hepatic fibrosis.

The only difficulty in distinguishing hepatic enlargement of this nature is in respect of the general enlargement which occasionally occurs when the organ is diffusely infiltrated with carcinoma. Such a liver at autopsy may show numerous nodules of growth which were not perceptible during life These cases can often be diagnosed by means of a puncture biopsy of the liver; but in the absence of this it may be necessary to wait until the growth of clinically evident nodules of cancer or the discovery of the primary tumour renders the diagnosis clear Splenomegaly is, of course, absent.

INTRINSIC INFILTRATIONS

Fatty Infiltration

When the term fatty infiltration is used without qualification it is taken, according to custom, to imply infiltration with neutral fat Enlargements of the liver due to such fatty infiltration may occur rapidly or slowly Occurring rapidly they may give rise to severe distension pain and to tenderness otherwise they are symptomless. Rapid enlargement may develop in two or three days under two conditions after certain poisons and in the precomatose stage of diabetes mellitus With the enlargement developing after poisons we are not concerned as the infiltration is incidental to the hepatic necrosis which, both pathologically and clinically, dominates the picture A slower, but still relatively rapid, fatty infiltration occurs after a period of intensive indulgence in alcohol It is usually symptomless, being discovered incidentally at autopsy on alcoholics who have

died either from accident[2 3] or suddenly and inexplicably;[5] but superimposed on an hepatic fibrosis it may cause an exacerbation of symptoms including jaundice. The great majority of enlargements due to fatty infiltration, however, and those which lead to diffuse hepatic fibrosis, are chronic conditions of long standing. These arise either from malnutrition or in association with chronic disease.

In temperate climates chronic fatty infiltration, without chronic disease, is most commonly found in alcoholics. Reasons have already been given for regarding this condition as due to dietary deficiencies *consequent upon alcoholism rather than as the result of a direct toxic* [illegible]

deficient in protein. Experimentally, protein deficient diets in themselves are capable of causing the condition and may well be the major causative factor in man As, however, the human diets are also deficient in other aspects the condition in man is often associated with, and may be in part due to, vitamin deficiencies. In the tropics children are [illegible]

the increased demand for lipotropic factors during growth far exceeding the supply of these in the deficient diet. But not all such cases survive to develop hepatic fibrosis. Many die from the condition itself, some from intercurrent illness, and others, suddenly and inexplicably, in a manner similar to that in acute alcoholism.

A fatty infiltration, frequently leading to diffuse hepatic fibrosis, has been observed in certain diseases of the nervous system. It is common in mongols, the infiltration arising during the second year, when *growth in such cases is unusually rapid, the fibrosis later.*[84] It also occurs in association with chronic increase of intracranial pressure.[54 85] Experimentally a similar sequence from fatty infiltration to diffuse [illegible] it was [illegible] almic [illegible] with increased intracranial pressure

Fatty infiltration of severe degree may occur as a *result of chronic* disease Diabetic patients who are imperfectly controlled over long periods often develop enlarged fatty livers and this may lead ultimately to classical diffuse hepatic fibrosis.[2] Similar infiltrations occur in chronic anaemias, but these rarely lead to the sequel of fibrosis

as the anaemia is either cured or kills the patient before this has time to happen. Lesser degrees of fatty infiltration are commonly found at autopsy on patients with cachexia or chronic febrile conditions. In these, however, the fat content of the liver is rarely high enough to cause damage.

Glycogen Disease[4]

This condition is characterized by an abnormal deposition of glycogen, and also of fat, in the parenchymal cells of the liver and occasionally in

enormously distorted with glycogen and it is usually because of the consequent symptomless enlargement of the liver that the child is brought under observation. Glycogen disease is one of the few
e liver, without
Many recover,
for long periods
and may develop diffuse hepatic fibrosis.[5]

EXTRINSIC INFILTRATIONS

The Lipoidoses

in xanthomatosis

Gaucher's disease is the commonest of the lipoidoses Tending to be familial it is so unobtrusive that it is not usually diagnosed till later childhood when the distended abdomen due to the large liver and spleen attracts attention. It is
symptomless, apart from a te
and sometimes skeletal pains
teristic tissue in the bones.
finding the characteristic cells in the material obtained by sternal or liver puncture. At death the Kupfer cells, and often the adjoining parenchymal cells, are distended with kerasin The changes of a diffuse hepatic fibrosis are present but not in such degree as to give rise to symptoms (Fig. 49)

Nieman-Pick's disease[7,8,9] is a congenital and familial condition

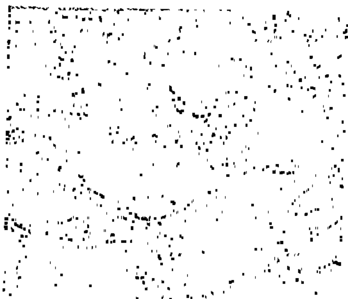


Fig 49—Gaucher's disease Man, aged 23 years Showing the diffuse hepatic fibrosis which develops in this condition Laidlaw's reticulin stain × 30



Fig 50—Experimental cholesterolosis Rabbit 2% cholesterol, high fat diet. The liver was extensively infiltrated with cholesterol Diffuse hepatic fibrosis was developing Laidlaw's reticulin stain × 42

rarely compatible with survival beyond early childhood. Gross en-

as a late development.

Xanthomatosis may be either secondary or primary.* The former occurs secondary to diabetes mellitus and may lead to enlargement of the liver and spleen from distension of the reticulo-endothelial cells in those organs with cholesterol. Primary xanthomatosis manifests itself in several forms. That involving the skin or the tendons, or that

changes are widespread in the liver (Fig 50). Deposits of cholesterol are said often to be present in the bile ducts and may then cause a symptomless, obstructive, jaundice. It is as yet uncertain in these cases whether the fibrosis is to be attributed to the infiltration or to biliary obstruction, or whether both factors play a part

The Reticuloses

Owing presumably to the relatively short life of those afflicted diffuse hepatic fibrosis has not been noted to develop.

Amyloid Disease

The infiltration in amyloid disease differs from those previously considered in that the infiltrating material is a substance, not normally formed in metabolism, and is deposited, not in hepatic cells, but in the walls of the small blood vessels Nevertheless the deposition is

to the majority of patients with amyloid disease dying of the condition, to which it is secondary, before fibrosis can develop

POST-INFILTRATIVE FIBROSIS

In patients who survive long enough, all the above infiltrations can lead to a diffuse hepatic fibrosis. The clinical features of this, when established, differ in no way from those of the similar fibroses produced by repeated zonal necroses of the liver. But there are two points which must be stressed here. Clinically manifest diffuse hepatic fibrosis due to infiltration, takes years to develop and, when the patient is first seen at the stage of hepatic fibrosis, the knowledge that his liver has been enlarged for years is a valuable point in indicating the nature of the process The second point is that even when the infiltration has been present for three or four years its removal may result in the reconstitution of an entirely normal liver. The following case illustrates this possibility.

A publican, aged 54 years, was first seen in 1927 He had had diabetes mellitus

cirrhosis of the liver with ruptured oesophageal varices. Actually the haematemesis had arisen from a symptomless duodenal ulcer, and the liver was soft and entirely normal both to macroscopic and microscopic examination From our knowledge of the pathology of the liver in diabetes mellitus it would seem probable that, during

stage [1]

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CHAPTER VIII

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CHAPTER IX

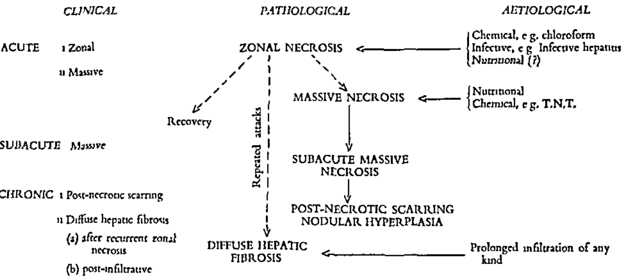
PARENCHYMATOUS HEPATITIS

ACUTE. i. *Zonal.*
ii. Massive.
SUBACUTE. Massive.
CHRONIC. i. Post-necrotic scarring (chronic massive hepatitis).
ii. Diffuse hepatic fibrosis (*a*) after recurrent zonal necrosis.
(*b*) after chronic infiltration.

In the above classification the term hepatitis is used in a broad sense to include all conditions in which there is widespread inflammatory damage to the liver parenchyma irrespective of the degree or stage of reaction to that damage. The classification is primarily clinical, the different illnesses being grouped according to the features they present to the physician. Nevertheless, the nature, and course, of hepatic illness being so closely dependent upon the underlying pathology, any clinical assessment must be related to the pathological lesion present, not only because this may provide a valuable clue as to the nature of the causative factor, but also because it provides the basis for the ultimate prognosis. These inter-relationships are shown in the table opposite and must always form the background of the clinician's attitude to the particular case.

ACUTE PARENCHYMATOUS HEPATITIS

The essential lesion in acute parenchymatous hepatitis is an acute degeneration of the parenchyma. In the mildest cases only minor degenerative changes are found, in more severe a centrilobular zonal necrosis develops, in the most severe the necrosis is massive in type. As has already been shown complete recovery from a single attack of zonal necrosis is always possible. But once massive necrosis has developed, whether this arise as a primary condition or as an extension of zonal necrosis, irretrievable damage has occurred and the case is committed to develop post-necrotic scarring. It is, therefore, of the utmost importance to decide whether the underlying lesion in a particular case is zonal or massive in type. Unfortunately such a decision


CLASSIFICATION OF PARENCHYMATOUS HEPATITIS
Clinical, pathological and aetiological inter-relationship
CLINICAL
PATHOLOGICAL
AETIOLOGICAL
ACUTE i Zonal
ii Massive
SUBACUTE Massive
CHRONIC i Post-necrotic scarring
ii Diffuse hepatic fibrosis
(a) after recurrent zonal necrosis
(b) post-infiltrative
ZONAL NECROSIS
Recovery
Repeated attacks
MASSIVE NECROSIS
SUBACUTE MASSIVE NECROSIS
POST-NECROTIC SCARRING NODULAR HYPERPLASIA
DIFFUSE HEPATIC FIBROSIS
Chemical, e g. chloroform
Infective, e g Infective hepatitis
Nutritional (?)
Nutritional
Chemical, e g. T.N.T.
Prolonged infiltration of any kind

is only possible during life in a minority of cases The symptoms and physical signs in all kinds of acute parenchymatous hepatitis are qualitatively similar and in most cases the particular lesion present can only be suspected from the severity or aetiology of the illness. At either extreme of the scale of severity are cases in which the nature of the underlying lesion can be deduced with reasonable probability, if not at once, then within the space of a few days. On the one hand are those severe cases with extreme parenchymal failure and profuse amino-aciduria together with those cases following exposure to hepatic poisons whose action is long delayed. Such have an underlying massive type of acute necrosis. On the other hand are those mild cases who have no sooner developed symptoms than they proceed to recover. A zonal necrosis or even milder degeneration of the parenchyma is the underlying lesion in these cases. But there remains a large group of intermediate severity in whom the precise diagnosis is not evident in the acute stage but only becomes apparent with the lapse of time. These latter all present with clinical features indistinguishable from those of a simple zonal hepatitis. Most recover, some flare into acute massive hepatitis; others smoulder along to subacute or chronic massive hepatitis *In describing the clinical features of acute* parenchymatous hepatitis, therefore, it is proposed first to outline the picture of hepatitis due to zonal necrosis and to indicate those deviations, clinical and aetiological, from the normal picture which would weigh in deciding whether a case of intermediate severity has, or has not developed, a massive hepatitis. The clinical features of outright acute massive hepatitis will then be described.

Acute Zonal Hepatitis

This condition is an acute illness of limited duration. *It produces* the symptoms of acute parenchymal failure, but its course is too short for the development of chronic failure. Jaundice is usually present, but in the mildest cases may be absent.[5] On examination the liver is [illegible]

The empirical tests of liver function are positive from an early stage in this as in any *form of acute parenchymatous hepatitis. An excess* of amino-acids in the urine is not found Recovery is often signalled by the occurrence of a diuresis.[334]

The duration of the illness depends upon two factors: the nature of

the causative agent; the presence or absence of a complicating massive hepatitis. If the agent is a short-acting poison the illness may last only for three or four days; if it is an infective agent, which remains active in the body for longer periods, then it may last for two or three weeks [illegible]
type [illegible]
suspec[illegible]
absence of other symptoms and signs, of a slightly enlarged, somewhat firm, liver with a smooth, regular edge, does not necessarily prove that massive hepatitis is present for, after a severe attack of zonal hepatitis, such an enlargement may take several months to subside. But the shorter the illness the more certain the diagnosis of zonal hepatitis The severity of the illness, and the immediate prognosis as regards survival, is correlated with the extent of the zonal necrosis [illegible]
rule.[5] Recovery from a single attack, when it occurs, is complete, and there are no sequelae; but repeated frequent attacks of zonal necrosis may lead to a diffuse hepatic fibrosis.[50, 59]

oc[illegible]
rel[illegible]
episodes are rare But further attacks within weeks of the original are relatively common Some show a curious association with external stimuli which has been noted too often for it to be dismissed as a coincidence Thus, shortly after apparent recovery, alcohol, exercise, or even jolting in a motor-car may be followed by a relapse.[3, 4] In others no reason can be seen. As a rule such relapses are not severe and complete recovery occurs. But that is not always so On two occasions I have seen death occur, and on others a progression to subacute hepatitis Some so-called 'relapses' undoubtedly represent the progressive manifestations of an original lesion whose severity has not been appreciated The majority, however, would seem to indicate either an abnormal, and unexplained susceptibility to stimuli which are ordinarily innocuous, or to a reactivation of the noxious agent.

Acute zonal hepatitis may be caused by chemical, infective and, possibly, nutritional factors. Hepatic poisons which produce their effects within a few hours of exposure characteristically lead to a zonal necrosis throughout the organ. Such are the chlorinated hydrocarbons. In general, these give rise to a mild illness, a limited lesion,

and recovery is the rule. Judging by the clinical features, and the survival without sequelae, hepatitis due to drug sensitivity is of similar

Fig 51—Hepatitis due to drug sensitivity Aminothiazole Data obtained during the second and third attacks of hepatitis in a case of thyrotoxicous receiving aminothiazole Each attack was signalled by pyrexia which immediately followed administration of the drug The case is reported below

type,[6] differing only in the length of time between exposure and the appearance of the illness, which time is presumably required for the sensitivity to the drug to develop. Doubt has been cast upon the existence of such a hepatitis, but the following case appears irrefutable.—

A woman, aged 37 years, suffered from thyrotoxicosis and was treated with aminothiazole Five weeks later she developed an illness which was indistinguishable from infective hepatitis Amino-thiazole therapy was stopped and the illness subsided in a month A test dose of 100 mg of amino-thiazole was then given The temperature rose to 100° F, but two neighbouring patients showed similar pyrexia, and, an infection being prevalent in the ward, it was discounted. Ten days later another test dose was given. The temperature rose to 101° F., jaundice appeared, the liver enlarged and the patient was gravely ill for six weeks It was then learnt that biliuria had been detected, but not reported, after the previous test dose (Fig 51)

Infective hepatitis, homologous serum jaundice, and jaundice after yellow fever vaccine, all give rise to an acute zonal hepatitis[16,33] usually mild in nature and from which recovery is the rule. Each is apparently due to an agent which has the characters of a virus but it is still uncertain whether the agent is the same in each case.[20,30,31,44] The condition presents as an acute and limited illness, and the long time which elapses between exposure to infection and the development of symptoms may justifiably be regarded as the incubation period of the illness. Liver biopsies have demonstrated two types of lesion; one centrilobular, the other showing both centrilobular and periportal distributions.[15] On

the basis of Gillman's work on the migration of iron pigment into the liver lesions of 'infantile pellagra'[27] and of experimental work on [illegible]

appear in experimental animals,[33] and its presence in samples removed[15] [illegible]

disease and that the periportal reaction, seen in some, is merely a later response to an initial centrilobular lesion. This view would accord with clinical experience, for it is known that the liver is affected some four or five days before jaundice appears in cases of infective hepatitis. In that period, the liver is enlarged and tender and gives rise to pain which, being epigastric, is usually attributed to 'gastritis'.[2] In epidemics many cases are detected at this stage and, of these, a considerable proportion subside without developing jaundice.[3 8 20 21 47 51 58]

Just as there are variations in the virulence of different poisons so there are variations in the virulence of the different infective agents The infective hepatitis group usually give rise to a mild illness with a limited zonal necrosis from which recovery is the rule. Comparable in severity to poisoning with phosphorus is the virus infection of Yellow Fever. This is usually said to give rise to a mid-zonal necrosis, but in the pathological material to which I have had access the disorganization of the lobule was so extensive as to have lost any zonal characteristics. The hepatic lesions in fatal cases of spirochaetosis ictero-haemorrhagica vary in severity from lobules with focal necrosis to lobules which are apparently normal save for evidence of biliary retention[12 13 40] It should be remembered that in this condition fatalities are more closely correlated with the severity of renal, rather than hepatic, functional impairment[10] and that, therefore, the milder degrees of liver damaged found at autopsy might well have been compatible with survival. Until a series of biopsies have been obtained from cases in the early stages of this condition the essential nature of its hepatic pathology will remain uncertain. Sequelae do not occur in the survivors of either yellow fever or Weil's disease.

A fulminant form of parenchymatous hepatitis occurs in which the [illegible]

developing cases of the lesion falling within the category of those massive necroses which arise from an extension of zonal necrosis. Such cases occur in the course of epidemics of infective hepatitis, when they may be attributable to the unusual virulence of the infecting agent or the supervention of a trophopathic hepatitis (Chapter V), or occur after exposure to certain virulent poisons such as the toxin of amanita phalloides [16] or phosphorus In support of the view that the pathology of these cases is essentially that of massive necrosis is the [illegible]

ciency, has been distinguished in man, but it is possible that such exists among races living on low protein diets, and will be found if sought. It is also possible that the zonal lesions found in fatal cases of the pernicious vomiting of pregnancy [60] may arise from nutritional deficiency. Patients with such lesions show the clinical features of an acute zonal hepatitis in that the survivors, even after deep jaundice, may recover entirely. The experimental work of Whipple,[43, 44] showing that protein depletion increases the severity both of the illness and of the pathological lesion after chloroform poisoning, has not yet found certain application in therapeutics. So far the majority of attempts at its clinical application have consisted in trying to increase the resistance of patients on diets containing normal amounts of protein, to such infections as infective hepatitis, by giving further protein.[9, 31, 32, 61] There is no basis in Whipple's work for believing that resistance in adequately nourished persons can be so enhanced. Nevertheless, indications are accumulating that this work may have clinical relevance. The infective hepatitis seems to be more severe, and the mortality rate many times greater, in malnourished than in well nourished populations [1, 30] In native races, living on low protein diets, infections such as lobar pneumonia, which in temperate climates rarely cause clinically evident zonal hepatitis, do so in a large proportion of patients.[45] Spectacular recoveries in desperate cases of infective hepatitis or homologous serum jaundice, whose nutrition has suffered from coma or severe anorexia and vomiting, are being reported after intravenous [illegible]

various illnesses are indistinguishable and in no way characteristic of the causative factor. The detection of the cause in an individual case

thus depends upon recognition of the general features of extra-hepatic effects peculiar to that particular causative agent.

Acute Massive Hepatitis

The diagnosis of acute massive hepatitis is usually made in retrospect. It may be strongly suspected during life, but the diagnosis cannot be made with certainty unless excessive amino-aciduria is demonstrable or the condition is revealed by puncture biopsy, or characteristic sequelae supervene. Acute massive hepatitis presents in two clinical forms. The first, in its early stages, is clinically indistinguishable from acute zonal hepatitis, and it is not till some days have elapsed that an exacerbation in the severity of the symptoms of parenchymal failure arouses suspicion. Anorexia and vomiting usually become marked. Jaundice deepens. A metallic taste is frequently noticed. Often the temperature and particularly the pulse rate begin to rise even in patients who have previously been afebrile. Epistaxis and haemorrhages from the alimentary tract, or into the skin, may occur But particularly ominous is the appearance of mental symptoms, which range from an incongruous euphoria, or manic delirium, to quiet coma. In the second clinical form the patient passes within a few hours from normal activity to the extreme stage of parenchymal failure without any preliminary period, in which the case resembles acute zonal hepatitis Often he is admitted in delirium or coma and so rapid may have been the onset of illness that jaundice may be absent. On examination of cases of this severity it may be found that a previously enlarged liver has decreased in size. Twitchings of the muscles, and rhythmical tremour, clasp-knife rigidity of the limbs and bilateral extensor responses to the plantar reflex may be present [184, 66] Examination of the urine is valuable. Urobilinogen is always, and bile pigments usually, present even where jaundice is absent from the integuments Most important, however, is the detection of an excessive amino-aciduria. This only occurs when necrosis of the liver is so extensive as to have left little functioning parenchyma When the amino-acids, leucine and tyrosine, are present in a [illegible]

the red blood cells and a subnormal level of urea together with raised values for ammonia and amino-acid nitrogen are important It should

be emphasized, however, that it is only in the severest cases that such chemical changes occur. Their detection usually indicates that death is imminent. In the majority of cases, and particularly those who do not die rapidly, such investigations yield results which are equivocal, and the suspected diagnosis must wait for confirmation on autopsy, or the subsequent development of the signs of subacute massive necrosis or post-necrotic scarring.

Acute massive hepatitis may arise as an apparently primary illness or in relation to acute zonal hepatitis. The justification for regarding *certain illness as being massive hepatitis from their inception is that,* as yet, all reported examples of these illnesses have had the clinical features and followed the course of such hepatitis and, although scattered zonal lesions have been found in their livers, particularly at the edge of areas of massive necrosis, no cases have been reported in which the lesion throughout the whole liver was of the uniform zonular type seen in acute zonal hepatitis. The best examples of primary massive hepatitis are seen after exposure to those poisons with delayed action such as trinitrotoluene[11, 33, 48, 49, 57] and cinchophen.[29, 38, 52, 55] The illness in such cases is usually of some weeks duration and the cases merge into those of subacute massive hepatitis, The possibility has already been considered that a similar illness may arise from a deficiency of protein, whether this be produced directly by an inadequate diet, or indirectly by drain of nutriments from the body, as in pregnancy, or by disordered metabolism, as in Wilson's disease or the de Toni Fanconi syndrome. All that can be said at present is that cases of massive hepatitis, without any trace of an origin in a zonal necrosis, do occur under such conditions in the apparent absence of any positive factor such as an infective agent or poison.

But in the vast majority of cases massive hepatitis arises on the basis *of an illness which normally gives rise to zonal lesion. Such a develop-*ment can arise under two conditions; as a result of the excessive virulence of the agent causing zonal hepatitis; because of increased susceptibility of the patient to an agent of ordinary virulence.

Chemical poisons causing an essentially zonal hepatitis, but whose virulence is such that the lesion extends through the whole lobule and becomes massive in type, have already been mentioned in relation to phosphorus and mushroom poisoning.[14] It is possible that, on [illegible] only zonal [illegible] Such seems [illegible] hepatitis [illegible]

Of the factors making for increased susceptibility to hepato-toxic agents only one is reasonably clear That is malnutrition; and the significance of this association, and the circumstances, direct and indirect, under which it may arise, have already been considered.

The prognosis of acute massive hepatitis depends upon the extent of the lesion within the liver as a whole. If generalized, death invariably occurs, and according to the length of survival 'acute yellow atrophy' or 'subacute red atrophy' will be found at the autopsy. If less extensive, the patient may go on to develop subacute hepatitis Restitution of the damaged liver to normal with complete recovery never occurs

SUBACUTE HEPATITIS

Subacute Massive Hepatitis

The lesion of subacute hepatitis is always massive in the areas affected Zonal hepatitis does not exist in a subacute form. Patients affected by zonal hepatitis either die or recover from the acute attack, or if the acute attacks are frequently repeated develop a chronic hepatitis in the form of diffuse hepatic fibrosis Subacute massive hepatitis appears in two clinical forms, as a sequel to acute massive hepatitis, as a condition which has been subacute from its beginning

Subacute massive hepatitis as a sequel to the acute type presents no difficulty In the acute stage there may have been doubt as to the nature of the lesion, but after several weeks the persistence of asthenia, slight jaundice and an enlarged liver begin to cause strong suspicions that the acute lesion was of the massive type, at least in parts of the liver, and is now in the subacute stage. These suspicions become a certainty on the appearance of signs of chronic parenchymal failure. The development of swollen ankles after exercise, of crops of pulsating spider telangiectases and of splenomegaly are ominous features The finding of a low plasma albumin associated with a high plasma globulin level, or a macrocytic hyperchromic anaemia resistant to liver therapy, confirm the d[illegible]

[illegible]

question of alcoholism, such cases are usually diagnosed as 'cirrhosis of the liver', but it is important to recognize them as a distinct group for their prognosis and aetiology are different The condition most commonly affects women, particularly after the menopause [5a, 32b]

Usually the presenting symptoms are vague. She may attend for advice because of her lack of mental and physical energy, or for anorexia, or for symptoms which suggest a neurosis rather than an organic disease. She may come up because of swelling of the ankles, shortness of breath on exercise, loss of weight, or repeated epistaxes. Rheumatic pains, without evidence of articular damage, are often noticed. Or she may delay attending until the condition has passed into the next stage of post-necrotic scarring and the manifestations of portal obstruction are superadded to those of chronic failure of the hepatic parenchyma. This latter type would appear to correspond to the cases called by Fiessinger[19] 'la cirrhose cicatricielle aigüe'. Sometimes the illness dates from an acute infection, such as a cystitis or a bronchitis, some one or two years previously. Since then she has never felt really well although with effort she has continued to work In a minority of cases the patient presents in an acute illness with jaundice, but examination reveals the presence of liver damage of a kind which must have preceded the present illness, and questioning elicits that symptoms, compatible with a liver disease, have been present for several months

On examination the patient is usually pale with muddy or slightly icteric conjunctivae. The skin is dull, the features drawn and the expression anxious. The breath may have the characteristic foetor. The palms and soles are often flushed and moist, and pulsating telangiectases may be present especially on the hands, forearms and forehead. In the more active cases a low grade pyrexia, with a corresponding elevation of the pulse rate, may be present. The patient is thin, although not usually to emaciation, but the general appearance of wasting is often camouflaged by distension of the abdomen and slight swelling of the legs The abdominal distension at this stage is more commonly due to gas in the intestine than fluid in the peritoneal cavity. The liver is enlarged, firm and not usually tender. Often the left lobe seems more enlarged than the right, causing a convexity forwards in the epigastrium The edge of the liver is thickened, gives the impression of coarse irregularity and inclines across the abdomen more horizontally than is normal. The edge cannot be sprung under the finger and attempts to do so rock the whole organ. The spleen is usually palpable and often grossly enlarged. Pitting oedema of the ankles is nearly always present even when the patient has remarked no swelling.

Taken together these findings justify the diagnosis of subacute massive hepatitis. The prognosis in such cases is death within one, two, or three years, according to the degree of parenchymal failure. The

case may progress steadily to the next stage of post-necrotic scarring or at any time an attack of acute hepatitis may supervene and cause death in a [illegible]
hepatitis. [illegible]
mate to tl [illegible]
the condi [illegible]
Figure 52 shows four consecutive areas along a single cylinder of liver obtained by puncture biopsy from a woman with subacute hepatitis of nine months duration. The lesions are indistinguishable from those already described for experimental 'subacute', (recurrent limited), massive necrosis (p. 71) At one end is the scar resulting from a localized, previous, massive necrosis, with its collapsed reticulum, cellular infiltration, proliferating bile ducts and formless groups of cells undergoing concentric hyperplasia Next are the areas with cellular infiltration and fibrosis in the portal tracts, but normal central veins, which represent lobules previously subjected to a more or less limited zonal type of necrosis Lastly comes the area, which escaped the acute lesion, where the normal lobular pattern survives. A year [illegible]
the condition was post-necrotic scarring or not. Only in the early stages of the lesion can the condition be identified with ease and certainty, at a later stage, when death ordinarily occurs, identification is often difficult and may be impossible. It seems, therefore, that the process [illegible]

The causation of subacute massive hepatitis presents several problems. [illegible]

lent, cases with the symptoms of subacute massive hepatitis tend to occur subsequently in patients who have shown no signs of the epidemic illness[3] It being known that during such epidemics cases of infective hepatitis without jaundice occur, the possibility must be entertained that some of the apparently spontaneous cases of subacute massive necrosis may be of this nature The recent epidemic in Denmark may well have been of this nature[59 326] A particular problem is, why do nearly all cases of subacute massive necrosis inevitably progress;

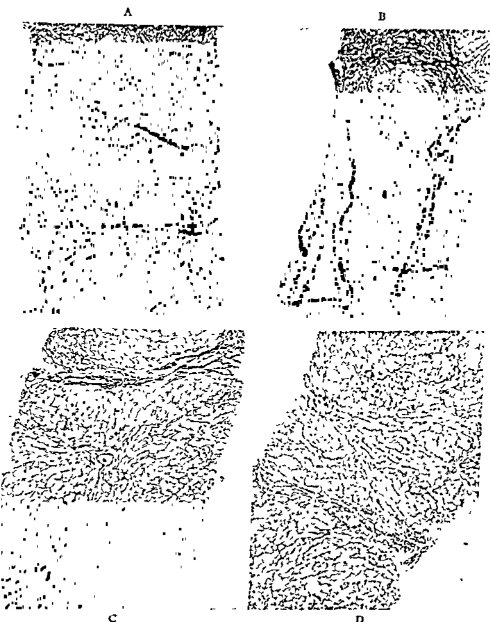


Fig 52

'Subacute' massive hepatitis Consecutive sections along a cylinder of liver obtained by puncture biopsy from a woman, aged 50 years Symptoms of 9 months' duration × 50 Laidlaw's reticulin stain

A

B

C

D.

why do not more become arrested? There are several possibilities; the progressive lesion may be an inevitable consequence of the initial damage, the causative agent may still be active, the original acute attack may have so damaged the liver as to render it unusually susceptible to noxious agents We have already seen that, when fibrosis of the liver has passed a certain stage, it progresses automatically even

[illegible]

causes only [illegible]
two or thre[illegible]
might remc[illegible]
from the study of homologous serum jaundice after blood or plasma transfusion, that a virus, capable of causing hepatitis, can survive in the body, but without producing ill health, for two or three years after an attack of hepatitis There is also evidence that malnutrition predisposes to severe liver damage from such a virus, and we have already suggested that extensive fibrosis may so interfere with the intra-hepatic circulation as to impair the nutrition of parts of the liver. It is conceivable that, if the initial attack were sufficiently severe to impair the hepatic circulation, a persisting virus might be able to attack the resulting ischaemic parts of the liver even though it were impotent to damage normal parenchyma If such were the case the progressive and vicious sequence of subacute hepatitis would be in train

CHRONIC HEPATITIS

Chronic hepatitis is the common termination of several pathological sequences and the first clinical evidence that it has developed in a case of liver disease is the appearance of signs of portal hypertension. It has been stated already that the most reliable of such signs is the demonstration of a collateral circulation between the portal and the systemic venous systems. The commonest and earliest site for these collaterals to appear is at the lower end of the oesophagus and, by means of radiology, these can be demonstrated long before their presence is indicated by such symptoms as haematemesis. The other manifestation of portal hypertension, ascites, is an unreliable sign, for several factors are concerned in its development and it may also appear in association with acute hepatitis.

When chronic hepatitis is established all hope of cure is gone. That is not to say, however, that death is imminent, for there are still considerable variations between the length of survival of different cases. Accidents such as haematemesis from the oesophageal veins may occur at any time without warning and cut short the patient's life, but, these apart, prognosis depends upon two broad considerations, the speed with which the condition has developed and the degree of parenchymal failure present. The faster the development of the condition, and the more conspicuous the signs of parenchymal failure at the time of diagnosis, the worse the prognosis, for, at the stage of chronic hepatitis, remissions do not occur and the lesion tends to progress at the speed with which it has been developing. Generally speaking the chronic hepatitis arising from necrotic lesions—post-necrotic scarring, or chronic massive hepatitis—progresses relatively rapidly, that arising from chronic infiltration—diffuse hepatic fibrosis—but slowly. It will be useful, therefore, to compare the typical clinical picture in each of these conditions, although it should not be forgotten that it is only the extreme examples of each which are in any way distinctive and that a large group of cases exists with syndromes of intermediate types, in which it is impossible to make an exact diagnosis until the autopsy is available.

Post-Necrotic Scarring (chronic massive hepatitis)

Post-necrotic scarring most typically develops as the sequel to sub-acute hepatitis, whether this arises as such or as an acute illness. On

clinical diagnosis. In chronic massive hepatitis the symptoms of chronic parenchymal failure long precede the signs of portal hypertension; in diffuse hepatic fibrosis the reverse is true or the two appear together. In chronic massive hepatitis the liver is usually enlarged and often its edge is so grossly irregular as to suggest secondary carcinomatous deposits. In *diffuse hepatic fibrosis the liver may be atrophic and*

impalpable and the edge, when felt, is seldom more irregular than to impart a sense of hard roughness to the finger. A history that the liver

massive necrosis it is usually moderately, and sometimes grossly, enlarged The differentiation of the two conditions is important both

The patient, a man aged 44 years, was admitted complaining of sudden swelling of the abdomen five days previously There was no history of alcoholism and the W R. was negative Three years previously, he contracted infective hepatitis during an epidemic of this disease This illness was unusual in that he remained jaundiced

the subcutaneous veins of the trunk were not enlarged. A lax ascites was present and through this a slightly enlarged, hard liver, with an irregular edge, and a moderately enlarged spleen were felt Pitting oedema at the ankles was present and

ture and pulse rose Ten days after admission he had a profuse haematemesis, lapsed

† Such fatty infiltration may have entirely disappeared by the time the patient comes to autopsy

The second patient was a woman, aged 35 years. Two years previously she had [illegible]

giectases A week later [illegible]
waist She th [illegible]
and on examir [illegible]
last four mon [illegible]
distended abd [illegible]
Ankle oedema was present By radiology oesophageal varices were demonstrated. [illegible]

persisted throughout At autopsy post-necrotic scarring with moderate nodular hyperplasia was found, the left lobe being more damaged than the right (Fig 33) Jaundice, and then only a tinge, was noted as a terminal event

Diffuse Hepatic Fibrosis

Most of the distinguishing features of the clinical syndrome associated with diffuse hepatic fibrosis have already been mentioned in order to point its distinction from chronic massive hepatitis. It remains only to stress the different natural histories of the two conditions.

Diffuse hepatic fibrosis often takes decades to develop and when developed it is compatible with further years of a reasonable degree of health. Not infrequently the lesion is discovered at autopsy, in patients who have died from other causes and who, at no time, have had any noticeable impairment of health referable to liver damage. In temperate climates the patient often is, or has been, an alcoholic and it is no uncommon experience to find a typically hard liver in such persons, when they attend for some other complaint Puncture biopsy of the liver is useful in such cases as it reveals the typical pattern of the fibrosis In the early, although not necessarily in the late, stages of the cases secondary to chronic fatty infiltration, it also reveals an engorgement of the parenchymal cells with fat. Evidence of acute hepatitis is conspicuously absent from their histories. Usually the patient first comes under observation with symptoms referable to portal hypertension. In contrast to cases of chronic massive hepatitis with similar symptoms, such cases with diffuse hepatic fibrosis are often not ill in themselves. They are incommoded by such symptoms as ascites, but they feel that if this were relieved they would have little complaint. There are few, often no signs of parenchymal failure. After they have recovered from their haematemeses, or their ascites has

been relieved by paracentesis, they leave hospital and resume their ordinary life. Thereafter they return from time to time, often at intervals of six months or a year, when their symptoms of portal hypertension have again returned. Eventually, if they do not die from some accident referable to portal obstruction, or contract an intercurrent illness such as pulmonary tuberculosis, they slowly develop

repeated attacks of acute zonal hepatitis; as a result of long continued infiltration of the liver of any kind When the former type occurs, as

Whether repeated attacks of a nutritional zonal necrosis occur or not

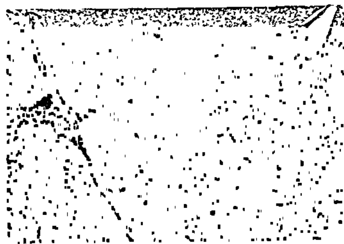
be said at present is that if such repeated attacks of nutritional zonal necrosis are shown to occur then it would be expected that this condition would ultimately lead to a diffuse fibrosis of the liver The chronic infiltrations which may lead to diffuse hepatic fibrosis have already been considered and the clinical similarity of livers so infiltrated to those with established fibrosis has been illustrated in the case of a diabetic patient The possibility must, therefore, be entertained

HEPATIC FIBROSIS OF DOUBTFUL AETIOLOGY

Any considerations of hepatic fibrosis must take into account two conditions whose causation is obscure, haemochromatosis and Banti's syndrome.

The hepatic fibrosis in haemochromatosis is of the diffuse type and it provides an opportunity for determining the natural history of this type of fibrosis when uncomplicated by a preceding infiltration. In haemochromatosis, fibrosis of the pancreas usually leads to diabetes mellitus before there are any signs of hepatic failure. Before the introduction of insulin such cases soon died of diabetes mellitus. Now it is possible to prevent this, and cases of haemochromatosis with fibrotic livers survive often for ten years or more without showing any symptoms referable to the liver.[51] Gillman[26 27 28] has recently shown that patients living on the abnormal native diets of the Rand may develop deposits of iron in the portal tracts similar to those in the cases of haemochromatosis seen in temperate climates; and that these iron deposits seem similarly capable of provoking a fibrotic reaction leading eventually to the production of diffuse hepatic fibrosis. Pancreatic fibrosis with diabetes mellitus does not, however, occur. This acquired condition he has termed 'cytosiderosis'.[28]

Few conditions have given rise to so much controversy as that of the liver and spleen described by Banti. Most physicians and pathologists are now agreed that it is not, as Banti thought, a single entity[17 18 41]



In a careful study, McMichael[33] showed that many cases so diagnosed during life proved at autopsy to be examples of other well-recognized

resemblance can be close, particul
in such cases. At autopsy, many
show typical post-necrotic scarrin

groups he considered a distinct entity.

THE CLINICAL SEQUENCES IN PARENCHYMATOUS HEPATITIS

It is evident that the different kinds of parenchymatous hepatitis may closely resemble each other in their clinical manifestations. This is not surprising, as pathological lesions, such as necrosis or fibrosis, are common to several of the different kinds, and it is to these lesions that the more obtrusive clinical manifestations are referable. Clinical differentiation thus depends upon attention to the less obvious, but more characteristic, manifestations, and the preceding considerations have been mainly concerned to display such, so that the different kinds of hepatitis may be recognized at each stage of their development.

development of diffuse hepatic fibrosis. Single attacks of zonal hepatitis do not cause permanent damage and recovery occurs; repeated attacks lead to diffuse hepatic fibrosis. Zonal hepatitis from unduly virulent agents may be virtually massive in type, or massive hepatitis may, under certain circumstances, supervene on any zonal lesion In either case the clinical manifestations and prognosis are those of acute massive hepatitis.

The classical sequence of massive hepatitis leads from the acute,

through the subacute, to the chronic stage of post-necrotic scarring and nodular hyperplasia. Cases starting as clinically evident acute massive hepatitis, if they survive the acute illness, usually run a relatively rapid course which rarely exceeds two or three years. But many cases do not start in this way. Some first develop symptoms at the subacute stage; others not until the stage of chronic massive hepatitis. In general the earlier in the sequence the condition becomes clinically evident the shorter the prognosis and the more obtrusive the signs of parenchymal failure. Thus, cases discovered in the subacute stage live little longer, after the diagnosis is made, than cases which start with the acute illness. But cases which remain latent until post-necrotic scarring and nodular hyperplasia have developed may live for several years. In them the predominant signs are those of portal hypertension and the normo- or hypochromic type of anaemia The usual manifestations of parenchymal failure are unobtrusive. If, as is usually the case, the spleen is conspicuously enlarged, they are indistinguishable from, if not identical with, cases of Banti's syndrome. These are the most common variants of the massive hepatitis sequence.

THE DIETETIC TREATMENT OF HEPATITIS

The role of malnutrition in exaggerating the lesions due to toxipathic agents and in producing the sequence leading from fatty infiltration to diffuse hepatic fibrosis has already been considered. The question remains as to the use of dietetic therapy in the treatment of established cases of hepatitis

[illegible] the sequence leading [illegible] If such infiltration is [illegible] levelop; if fibrosis is already established then removal of the excess of fat from the paren- [illegible]

the diet supply al [illegible]
140 g. of protein [illegible]
a diet containing [illegible]
addition they advise that 50 g. of yeast be given daily to supply *B* vita- [illegible]

has been demonstrated.

In western countries the majority of cases showing this particular sequence of hepatic damage are alcoholics and it has already been pointed out that the development of the hepatic lesion in such cases can best be explained as the result of the malnutrition consequent upon alcoholism rather than as a direct toxic result of alcohol itself. It goes without question that, before attempting to remedy the malnutrition, the agent inducing it—alcohol—must be given up But whether the dietary deficiency arises from direct starvation or indirectly

the other is the result of the impaired synthetic capacity of the liver consequent upon the hepatic lesion The effects of the first, such as starvation oedema, are rapidly removed by an appropriate diet and it is perhaps for this reason that the most dramatic effects of dietetic therapy have been recorded in the fatty-infiltration diffuse, hepatic fibrosis sequence[49a, 49b] which is directly associated with dietary deficiencies But the same treatment will also remove fat from the liver and coincidentally, induce an improvement in hepatic efficiency.[11a] It is because of this latter effect that dietetic treatment in this condition can justifiably be regarded as specific therapy, and to it may be attributed the sustained improvement and, in early cases, the apparently permanent benefit which follow its continued application

Compared with these encouraging results those obtained in cases of chronic hepatitis due to post-necrotic scarring are disappointing[49b]

be avoided

The theoretical considerations, which underlie the dietetic therapy of acute and subacute hepatitis due to toxipathic agents, have been outlined in chapter V. It has been seen that, although there is good evidence that hepatic parenchymal cells depleted of protein and tocopherol are unduly susceptible to noxious agents, there are no grounds

shall be in the best possible condition to resist any further spread of the lesion. Now clearly nutritional deficiency of the parenchymal cells may arise in two ways from inadequate amounts of the necessary nutriments being available within the body, either because of inadequate intak [illegible] ng normal, from the circulation [illegible] by such morbid processes as par [illegible] depleted of the necessary nutriments before it has travelled more than a little way down the hepatic sinusoids In the first case the need is to remedy the depletion; in the second to surcharge the blood with the factors required The same measures serve both ends. They are to maintain, at all costs, the necessary intake of protein and to supply sufficient calories to ensure that this is utilized for its specific purposes rather than burnt to supply energy. In addition the accessory food factors, such as [illegible]

tak [illegible]
by
suit
soluble casein. Should the appetite fail the physician must have no hesitation in resorting to artificial methods of feeding such as the continuous intra-gastric drip. If the condition deteriorates then appropriate intravenous therapy should be considered Of such plasma transfusions have given the best results.

The beneficial, although temporary, effect of plasma transfusions can best be demonstrated on cases with chronic parenchymal failure who have reached the stage when they are becoming drowsy. Amounts of the order of 75 g of dried human plasma must be given daily for several days and an adequate intake of carbohydrate maintained by mouth. The increased wakefulness of the patient, the improved appetite and the renewed sense of well-being may be quite striking. Such patients usually have hypoproteinaemia and oedema. How much of the improvement is due to the loss of such oedema consequent upon elevation of the plasma proteins is difficult to judge, but Kunkel and his colleagues[326] believe that the improvement cannot all be attributed to this and cite cases in whom a sustained remission occurred after transfusions of concentrated human serum albumin. Plasma transfusions in these quantities have also been given to desperate cases of acute

massive hepatitis. Dramatic recoveries have been reported in some but, as equally dramatic recoveries occur spontaneously, no opinion on the value of such treatment can be expressed. In practice, however, any remedy which holds out the faintest hope of benefit to these cases

preliminary trials, on admittedly severe cases, no conspicuous benefit has been noted.

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CHAPTER X

CHOLANGIO-HEPATITIS, OBSTRUCTION TO THE BILE DUCTS, AND BILIARY DIFFUSE HEPATIC FIBROSIS

THE syndrome due to uncomplicated biliary obstruction has already been considered. In order to distinguish it, it was necessary to exclude all cases showing clinical evidence of infection. The remarkably mild impairment of health consequent upon a simple retention of bile was then evident In the majority of patients with biliary obstruction, however, the illness is more serious and, as a general rule, it can be stated that the seriousness of the illness is proportional to the severity of the accompanying infection. In the most severe cases there is no difficulty in demonstrating that this infection arises in a cholangitis, for at autopsy the biliary tracts are full of purulent bile and macroscopic or microscopic abscesses are present in the region of the portal spaces. [illegible]

clinical evidence of infection, a similar though less marked inflammatory reaction is present It is apparent, therefore, that in man some degree

chyma

appears

major clinical features of most cases are due This view is strengthened by observations on those infrequent cases of cholangitis without demonstrable obstruction to the large bile ducts. Such are clinically indistinguishable from cases with painless biliary obstruction and, pathologically, the changes in the liver are identical with those in obstructive cases with cholangitis of comparable severity. It would seem, therefore, justifiable to suggest that our attitude to lesions of the biliary tract should be reorientated. Cholangitis—or to speak more accurately, cholangio-hepatitis—would then be regarded as the central condition; mechanical obstruction to the large bile passages, if present, as a predisposing cause to this

THE PATHOLOGY OF CHOLANGIO-HEPATITIS

The pathological changes in cholangio-hepatitis vary greatly according to the severity of the inflammatory process in and around the smaller bile ducts. At one extreme are the overwhelming infections causing suppurative cholangitis, at the other the chronic mild processes, lasting for years, leading to 'biliary cirrhosis'. But although *these two conditions exhibit such conspicuous differences in their* pathological features and clinical manifestations, they represent but extreme degrees of the same process and all gradations from the one to the other may be correlated with the severity of the inflammatory process present. The extent to which the lobule is involved is clearly so correlated. So is the speed with which the lesion develops. Further, the extent of the lesion within the lobule indirectly determines the stage of inflammatory reaction found at autopsy for, when parenchymal damage is extensive, death occurs from parenchymal failure before the inflammatory changes in the liver have fully matured In discussing
tis, therefore, it is con-
process according as to
mild, such distinctions
corresponding to the clinical syndromes of acute, subacute or chronic *cholangio-hepatitis. It should be clearly understood, however, that* these distinctions are purely for convenience and imply, not the existence of separate and distinct entities, but simply degrees in one series.

Severe cases of cholangio-hepatitis die rapidly, usually from the effects of the infection itself. The condition has long been recognized
cholangitis. At autopsy
It is usually fatty and, if
bscesses may be seen under
the capsule and on the cut surface, and purulent bile exudes from the bile ducts Evidence of septicaemia is present in other organs. On microscopic examination dense masses of neutrophil leucocytes are present in the portal tracts and extend into the surrounding parenchyma. The contiguous parenchyma and many of the leucocytes are degenerating. The smaller bile ducts have usually disintegrated and the larger ducts contain inflammatory cells (Fig. 56).

Suppurative cholangio-hepatitis may occur in a hitherto healthy organ or it may be superimposed on a more chronic form of cholangio-

hepatitis, particularly one in which obstruction to the large bile duct has long been present.

The moderately severe infections of the bile ducts give rise to a subacute illness compatible with survival for many months or even two or three ye

its shape.

granular.

quence the liver also is pigmented; in the early stages being brown with a greenish tinge, in the later resembling shagreen leather (Fig 54). Early in the course (Fig 55a) microscopic examination shows a profuse cellular infiltration spreading out from the portal tracts, mainly towards neighbouring portal tracts, but also into the adjoining parenchyma so as to isolate individual liver cells. The cellular exudate con-

tion of the bile ducts is conspicuous. In the later stages (Fig. 55b) the

(Figs. 55b, 66b). Such subacute cases usually die of parenchymal failure, or of a superimposed acute cholangio-hepatitis, before the changes in the liver have had time to progress to the stage of unequivocal 'biliary cirrhosis.'

Mild cases of cholangio-hepatitis may endure for years In the early stages the liver appears grossly normal apart, perhaps, from a slight enlargement. Microscopically changes are almost confined to the portal tracts seldom involving more than a layer or two of the imme-

[illegible]

is that the portal tracts stand out conspicuously as fibrous islands in the liver parenchyma (Figs 58, 60a and b). Should infection become more severe at any stage, the process spreads more widely and rapidly, as in the subacute type, and the tendency for fibrosis to develop between the portal tracts and circumscribe the lobules becomes evident.[2,3,7,17] In such mild cases there may be no retention of bile but, if retention does occur, the bile pigment will be found mainly in the cytoplasm of the centrilobular cells. By the continuation of this insidious process chronic cholangio-hepatitis, or 'biliary cirrhosis', is produced The livers from such cases have a finely granular surface and are either yellowish brown or green according as to whether jaundice was present or not. Both liver and spleen are enlarged, but their peritoneal coverings are less thick than in the subacute type and adhesions are usually few Ascites and evidence of portal obstruction are unusual

[illegible]

sis circumscribes but rarely invades the individual lobules, the centrilobular vein is not involved in the process (Fig. 60) and the normal intralobular pattern remains intact. Parenchymal regeneration nodules are not a feature of such fibroses,[1,2,11,17] but, in the portal tracts and fibrous septa, numerous worm-like bile ducts are present and the larger ducts are usually dilated and surrounded by a thick ring of fibrous tissue

In specimens from cases of cholangio-hepatitis, obtained at autopsy, a centrilobular necrosis is often found By comparison with specimens obtained at operation a few days before death it is evident that such necrosis is a terminal event and not an essential feature of the process. It may well be the result of a failing circulation in a liver through which the blood-flow is impeded by inflammation or fibrosis in the portal tracts.

These considerations bring out clearly that the degree and speed of development of the lesion in cholangio-hepatitis is dependent upon the

[illegible]

and diagnostic importance in the clinical consideration of cholangio-hepatitis, can be related to the degree of this parenchymal involvement.

Aetiology of Cholangio-hepatitis

[illegible]

incision of the duct, is a less common cause Inside the liver, obstruction to the larger bile passages may arise from similar causes—stones, [illegible]

tion of the ducts behind the block.

In acute suppurative cholangio-hepatitis, and in many cases of the subacute type, bacterial infection of the bile can be demonstrated. Usually the infecting organism is B coli but sometimes, especially in subacute cases, streptococcus viridans is found. In the milder cases the bile is commonly sterile, but this cannot be taken as proof of the consistent absence of infection, for the course of cholangitis is notoriously intermittent. The route by which infection gains access to the biliary tract is, as yet, uncertain. Some have thought that the organisms ascend the bile passages from the gut. Others, that they are excreted in the bile.[13, 15] The experiments of Wilkie[15, 16] indicate that such excreted bacteria do not normally give rise to inflammation of the biliary tract if the bile is flowing freely But if the flow is obstructed, cholecystitis and cholangitis develop.

THE CLINICAL TYPES OF CHOLANGIO-HEPATITIS

[illegible]

examples, acute suppurative cholangio-hepatitis and biliary hepatic fibrosis, are so dissimilar that if one were unacquainted with the intermediate varieties it would be difficult to see the relation of the one to the other. For this reason it is most convenient, first, to describe a type of intermediate severity and duration, which, though not common, shows the particular clinical features of cholangio-hepatitis

in their most well-developed form. The other varieties can then be briefly illustrated by reference to their points of difference.

Subacute Cholangio-hepatitis

The following case shows the main features and course of this type.

[illegible]

jaundice There were no signs of parenchymal failure and the temperature and pulse rate were normal The liver was uniformly enlarged to the level of the umbilicus It was smooth and the edge was firm and could be sprung under the fingers The spleen was not felt The plasma protein level was normal; there were 8000 leucocytes per c mm , but the serum contained 4·2 mg. of bilirubin After her admission the temperature began to rise slightly more each evening until it reached 100° F. Thereafter it declined by slow lysis to normal. The pulse was hardly affected Coincident with the rise of temperature the jaundice deepened, the abdominal pain became

[illegible]

She felt well and her appetite returned Ten days later the temperature began to rise

[illegible] further bout [illegible] consented [illegible]

[illegible] A biopsy was taken from the liver and showed a moderately severe cholangio-he[illegible]

[illegible]

101° [illegible] more, the liver enlarged down to the right iliac crest and remained tender and painful. Throughout this period bile continued to drain from the wound and at various times B coli, strep. faecalis, and B. pyocyaneus were grown from samples taken from far up the fistula. Thereafter for two months she was afebrile Her liver ceased to be tender but remained grossly enlarged, and the jaundice was unaltered Bile, however,

[illegible]

Six months later she was readmitted Haemoptyses had occurred and pulmonary tuberculosis had developed Her previous symptoms were all present, but more

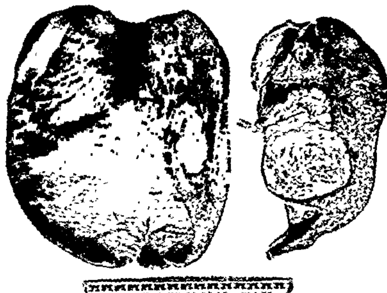


FIG 54—Subacute cholangio-hepatitis from chronic biliary obstruction due to a papilloma of the bile duct Weight of liver 3,100 g Left lobe of the liver The left hepatic duct has been dissected out and the site of constriction is indicated by a bristle The case is described on p 190 Twenty-two months elapsed from the onset of jaundice to death The diffuse fibrosis is shown in Fig 55B Despite the widespread fibrosis the surface of the liver is only finely granular

marked Slight swelling of the ankles had been persistent. Although cheerful the patient felt ill. The temperature rose to 102–103° F each night. On examination the conjunctivae were deeply jaundiced but the skin showed a generalized sepia brown pigmentation. Oedema of the ankles was present but only a few inconspicuous telegiectases Clubbing of the fingers had developed No ascites nor enlarged collateral veins were detected The lymph glands throughout the body were moderately enlarged The liver now filled most of the abdomen Its lower edge was thick and it could not be sprung with the finger It was not irregular The spleen projected a hand's breadth below the costal margin The most noteworthy changes in the blood were that the serum bilirubin had risen, and remained between 12 and 16 mg /100 cc , and a macrocytic anaemia had developed She remained in hospital for a further four months, during which time her symptoms remained unchanged, and finally died, twenty-two months after the first onset of jaundice, with a severe colitis

At autopsy a large fine granular liver, the surface of which looked like green shagreen leather was found It weighed 3070 g It was firm, and fine bands of fibrous

tissue could be seen round the lobules, but there were no coarse scars. The extra-hepatic bile passages were normal, but on cutting into the liver a tumour about the

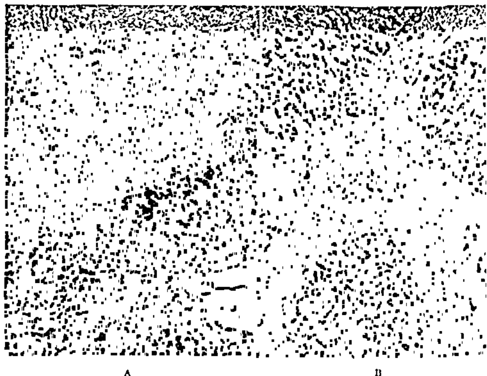


Fig 55—Subacute cholangio-hepatitis due to chronic biliary obstruction consequent upon a papilloma of the bile ducts Case described on p 190 H and E × 65

A

B

The salient features of this case are the periodic attacks of fever and jaundice and the delayed appearance of signs of parenchymal failure.

The early febrile attacks were typical. During them the jaundice [illegible]

bile returned to the stools and diminished in the urine. The liver decreased in size and became painless. The patient now felt comparatively well. But with the subsidence of each succeeding febrile attack the residual evidence of damage was a little more pronounced until eventually signs of chronic parenchymal failure began to appear. This is the clinical picture of subacute cholangio-hepatitis. Presumably what happened was that the tumour caused only incomplete obstruction of the hepatic ducts. When an exacerbation of the cholangitis occurred the epithelial lining of the ducts swelled and produced complete obstruction. When the attack abated the passages again became patent. It might be contended, however, that the gradually increasing failure of the symptoms of obstruction to disappear after each febrile attack might be due to the tumour growing and so producing more complete obstruction That this explanation is unnecessary is shown by the following case.

A woman, [illegible] grown in pure culture from the bile After some weeks she left hospital, to be re-admitted eight months later after an accident The periodic pyrexia with jaundice had continued. She died from this accident three weeks later, one year after the onset of jaundice At autopsy no evidence of past or present obstruction to the large bile ducts was found The macroscopic and microscopic appearance of the liver were those of subacute cholangio-hepatitis

There are many detailed features in such cases which are of interest, but [illegible]

Further, the pulse is less accelerated in relation to the fever than would be expected. The erythrocyte sedimentation rate, however, is usually high

Acute Suppurative Cholangio-Hepatitis

This condition is similar to the exacerbations of subacute cholangio-hepatitis save that the infection dominates the picture. Septicaemia is present and its high temperature, rigors and general symptoms over-

shadow the liver damage. Jaundice, the pain of perihepatitis and an enlarged tender liver are, however, usually present. The condition

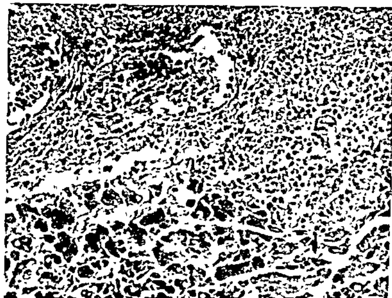


FIG 56—Suppurative cholangio-hepatitis Woman, aged 39 years, carcinoma of *the cystic duct spreading into the common bile duct High fever and jaundice Post-*mortem specimen The portal tracts and bile ducts are crowded with neutrophil leucocytes H and E × 200

practically always arises secondary to obstruction. Its course is necessarily short (Fig. 56).

Intermittent Acute Cholangio-Hepatitis

This form of cholangio-hepatitis is characterized by bouts of fever, of a few hours' duration, which are often ushered in by a rigor [2] A remarkable feature of these attacks is that, although the patient may be disorientated, or even delirious, at the height of the fever, within a few hours of the temperature falling he is entirely normal again This is in marked contrast to the similar attacks which may occur in the comparable condition in the kidneys, suppurative pyelo-nephritis,

[illegible]

sive days, or, rarely, more than once a day (Fig. 57); or, in the early stages, they may be separated by intervals of several weeks. They may

occur as an initial symptom, shortly after a gall-stone has lodged in the common bile duct; or they may supervene on a chronic form of

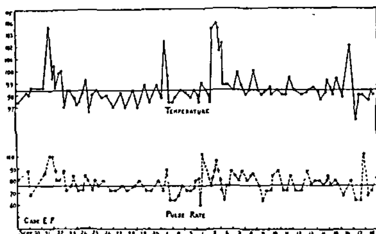


FIG 57—*Intermittent fever in cholangio-hepatitis* From the case of a woman, aged 51 years, with gall stones in both intra- and extra-hepatic bile ducts

cholangio-hepatitis In the former case it is unusual for them to be repeated and they are often associated with jaundice In the latter, jaundice is usually conspicuous by its absence In themselves they do not seem to cause gross liver damage. Hepatic pain is mostly lacking, signs of parenchymal failure are not found, and gross enlargement of the liver if present, is due to the condition they complicate. I have never seen this form of cholangio-hepatitis apart from obstruction of the large bile ducts The following case is typical.

A woman, aged 76 years, was operated upon eight years previously for empyema of the gall bladder and a year later the remnants of the gall bladder were removed The liver was not fibrotic then At no time was she jaundiced She remained well for six years, then she began to have shivering attacks about once a week The shivering lasted a few minutes and then she became 'unconscious' and incontinent of urine

diately after the rigor it was 11,000 per c mm The erythrocyte sedimentation rate

shadow the liver damage. Jaundice, the pain of perihepatitis and an enlarged tender liver are, however, usually present. The condition

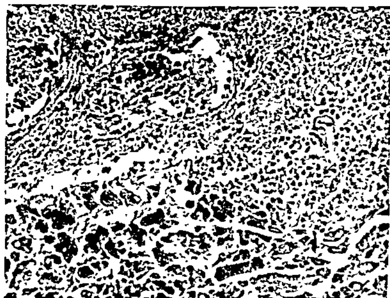


FIG 56—Suppurative cholangio-hepatitis Woman, aged 39 years, carcinoma of the cystic duct spreading into the common bile duct High fever and jaundice Post-mortem specimen The portal tracts and bile ducts are crowded with neutrophil leucocytes H and E × 200

practically always arises secondary to obstruction. Its course is necessarily short (Fig 56).

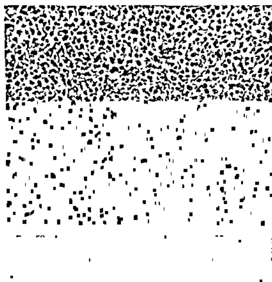
Intermittent Acute Cholangio-Hepatitis

This form of cholangio-hepatitis is characterized by bouts of fever,

few hours of the temperature falling he is entirely normal again This is in marked contrast to the similar attacks which may occur in the comparable condition in the kidneys, suppurative pyelo-nephritis, where the patient remains profoundly ill. The clinical features suggest

fibrosis, it would have no practical importance. The following kind of case will be familiar to all.

The patient was a woman, aged 64 years, admitted complaining of jaundice and itching for five weeks She looked healthy and cheerful The liver was uniformly



enlarged to two fingers' breadth below the costal

The following case illustrates the results of such a cholangitis when of long duration.

The patient was an active man, aged 80 years One evening he had what he

jaundiced nor was there bile in the urine At operation a solitary calculus was found lying loose in the common bile duct Biopsy of the liver showed fibrous tissue linking neighbouring portal tracts He made an uninterrupted recovery and his health is again enviable

a few days It was, therefore, decided to operate and at operation a large gall-stone was found lying free in the common bile duct. This was removed but the patient



FIG 58—Intermittent cholangio-hepatitis Man, aged 63 years Stone in common bile duct Rigors followed by pyrexia of several hours duration, occurring about once every 10 days, for 15 months Biopsy specimen H and E × 55

died six days later At autopsy the liver weighed 1500 g It was grey in colour, finely granular and tough in consistency No obstruction to the bile passages was found Microscopic examination showed a diffuse hepatic biliary fibrosis with a superimposed acute cholangio-hepatitis (cf Fig 58)

Mild Cholangio-hepatitis

This type of cholangio-hepatitis (Fig. 59) is insufficient to give symptoms other than fever. Its existence is only revealed by the temperature flickering up to 99° F or thereabouts in the evening, either persistently or from time to time. It is the type commonly associated with biliary obstruction due to carcinoma of the head of the pancreas. Such cases are in general assumed to be apyrexial, but examination of the temperature records of patients who have been under observation for two or three weeks rarely fails to show some elevation. This is the commonest type of cholangitis, and, were it not for the fact that it could develop into the more serious form, or lead to an hepatic

extra-hepatic bile ducts Biopsy of the liver showed a diffuse hepatic fibrosis (Fig. 60) with neutrophil infiltrations round the larger bile ducts The patient made a slow recovery but the jaundice was still present when she left hospital after two months [illegible] tococcus was found after 11 days incubation but this died out, despite subculture, in two days, so that it could not be identified Her physical state was essentially the same

[illegible]

and hepatic ducts The liver weighed 1890 g, the spleen 750 g Ascites and signs of portal obstruction were absent Histological examination of the liver showed the same picture as in the previous biopsy

It is evident that, in the above case, the fibrotic condition of the liver found at the operation could not have developed in the preceding two months during which jaundice was first noted. The subsequent post-mortem findings substantiate the diagnosis of biliary hepatic fibrosis It seems, therefore, that this fibrosis must have developed insidiously in the period between her first operation at the age of 35 years and her first coming under our observation fourteen years later. The case histories recorded under the heading of mild cholangio-hepatitis show that such cholangitis may persist for long periods without disabling illness, and without jaundice, and yet may be sufficient to cause fibrotic changes in the liver

HANOT'S 'HYPERTROPHIC BILIARY CIRRHOSIS'

Any one reading the account of the case of subacute cholangio-hepatitis secondary to obstruction of the bile ducts by an intrahepatic papilloma must have been struck by the similarity of its clinical features to those described by Hanot[5] as characteristics of the condition he called 'hypertrophic biliary cirrhosis' But for the finding of obstruction at autopsy it would have passed for a classical case of Hanot's cirrhosis

At this distance in time it is [illegible] tive biliary cirrhosis of Charcot[2] The essential feature of the former was believed to be atrophy, of the latter, hypertrophy of the liver Keen controversy existed as to whether a non-obstructive cirrhosis

But it is possible that similar degrees of cholangitis occur apart from biliary obstruction.

A woman, aged 60 years, began to sweat at night and feel generally tired some three months before admission to hospital. It was then noted that her temperature rose to [illegible]

agglutinin reaction But her erythrocyte sedimentation rate was 40 mm/hr One [illegible] nder liver [illegible] The gall [illegible] n the gall bladder was removed and the bile ducts, which were not dilated, were explored No stones apart from that present in the gall bladder and no obstruction of any kind was found After operation iodized oil was injected down the drainage tube into the bile ducts It passed freely into the duodenum and up towards the liver Cultures of the bile drawn at operation were sterile A biopsy of the liver showed an inflammatory [illegible]

Chronic Cholangio-hepatitis
(Diffuse biliary hepatic fibrosis)

Diffuse hepatic fibrosis consequent upon biliary obstruction takes some years to develop to the stage of giving clinical symptoms. In consequence it is not seen in cases with pronounced infection for in them death occurs, either from infection or parenchymal damage, before fibrosis can develop. The form of cholangio-hepatitis in which it occurs is one in which infection smoulders and in which obstruction if present is slight. For these reasons jaundice is usually absent throughout most of its course. The following case illustrates its usual features.

A nurse, aged 49 years, had been operated upon 14 years previously for gall-stones She was then jaundiced and before the operation had pain after meals After the operation all the symptoms disappeared Two months before admission she was suddenly wakened by a severe attack of pain over the right lower ribs Next morning she was told that she was jaundiced, and this became deeper over the next few days The patient was a nervous woman who had evidently lost much weight Slight [illegible] he admitted that her ankles [illegible] also was enlarged to a [illegible] Ten days later she had a [illegible] Operation was agreed [illegible] in diameter uniformly [illegible] sions covered the organ [illegible] impossible to reach the

could ever be hypertrophic; and in that atmosphere Hanot announced the discovery of a new type of non-obstructive cirrhosis in which hypertrophy was a leading feature. It is no wonder that Hanot's thesis was welcomed, for it served to quiet those who questioned whether alcoholic cirrhosis was always atrophic. But even so, Hanot was so imbued with current theory that he felt it necessary to suggest that in his cirrhosis the fibrous tissue differed from that in Laennec's in being unable to contract! If one examines Hanot's original thesis

hyperplasia had been distinguished.[12] His pathological criteria are also open to question. The majority of his cases seem to have died in the summer In those days there was no refrigeration, and often two or three days elapsed between death and the autopsy. It is not, therefore, surprising that with further experience difficulty has been found in recognizing, in all its clinical and pathological details, a condition fulfilling the requirements laid down by Hanot.[13] What now seems evident is that the clinical syndrome Hanot abstracted from his varied series of cases was the syndrome of subacute cholangio-hepatitis, whether this arise secondary to obstruction or not.[8] As such the syndrome is not peculiar to one disease entity nor is it essentially a chronic hepatitis On the contrary, it is a cholangio-hepatitis and requires to be recognized and treated as such

'CHOLANGITIS LENTA'

In 1921 Schöttmuller[14] suggested that just as the *streptococcus viridans* may attack the heart valves, and give rise to the septicaemia of subacute bacterial endocarditis, so it may attack the bile ducts and give rise to low grade cholangitis with septicaemia[6] Outside Germany this conception has found little support and La Manna[10] has critically examined the reported cases. Most had some source of obstruction in the biliary tract, the streptococcus viridans was recovered from only a few, and organisms, especially B. coli, were recovered from others. It would seem that there are no good reasons for regarding these cases of cholangitis as different from those already recognized.

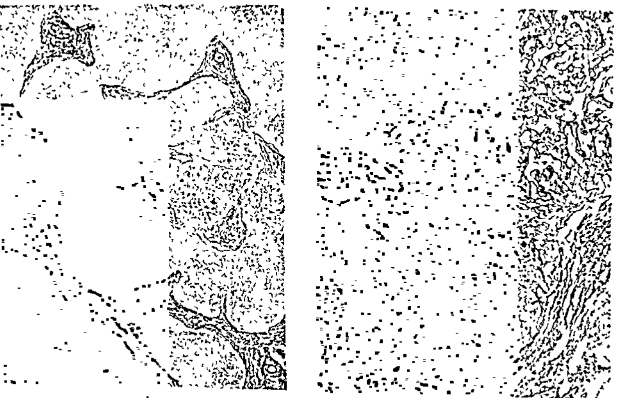


FIG. 60.—Chronic cholangio-hepatitis. Biopsy specimen. Woman, aged 49 years. Cholecystectomy for gall stones 14 years previously. Admitted with slight jaundice and temperature. *Found to have enlarged hard liver.* Died 15 months later and at autopsy found to have gall stones in both intra- and extra-hepatic bile ducts. Laidlaw's reticulin stain. A × 14. *The fibrosis is centred on, and in many places limited to, the portal tracts.* B × 65. The fibrosis is limited to the portal tracts and the periphery of the lobule. Each lobule is so circumscribed. Within the lobule there is no excess of fibrosis, the hepatic veins being entirely normal.

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GENERAL CONSIDERATIONS ON CHOLANGIO-HEPATITIS

The varying clinical syndromes attributable to cholangio-hepatitis have now been outlined It is evident that the condition can exist with or without jaundice, or hepatomegaly or parenchymal failure Its course may be as fulminant as a septicaemia and the patient correspondingly ill Or it may be so insidious that the patient is hardly aware that he is not healthy In the absence of evidence, such as jaundice, pointing to the liver it is difficult to recognize As the hepatic parenchyma is contiguous with the bile ducts a greater or lesser degree of hepatitis is present in each case. But this is a later development, so that in cholangio-hepatitis the symptoms of hepatitis, when present, are delayed for some time after the onset of illness. This is well seen in obstructive cholangio-hepatitis with jaundice. There the sense of subjective illness is delayed for some time after the patient becomes icteric, while in conditions, such as infective hepatitis, in which inflammation of the parenchyma is the primary event, this sequence is reversed. Cholangio-hepatitis can occur with or without obstruction. On clinical grounds it is impossible to be certain that obstruction is absent All cases diagnosed as cholangio-hepatitis should, therefore, be explored surgically

by failure to remember this point. In cholangio-hepatitis, as in any other variety of hepatitis, parenchymal failure can occur and, not infrequently, this seems to be precipitated by major operative procedures Anorexia is a common result of the conditions which lead to cholangio-hepatitis and, by the time the patient comes under observation, the intake of food may have become significantly inadequate. Efficient pre- and post-operative dietetic treatment of such cases is always a major consideration and should be instituted whether clinical signs of malnutrition are present or not. Even in those patients in whom the liver has been so damaged that surgical relief of the obstruction cannot ensure recovery, appropriate and persistent dietetic therapy, combined with control of the cholangitis by chemotherapeutic or antibiotic therapy, may lead to a considerable amelioration of their condition. The lines of the dietetic therapy indicated have already been discussed in relation to parenchymatous hepatitis

of a diseased vessel to which a collateral circulation has partially, but not completely, developed [9, 11, 13, 14, 20]

Acute and complete occlusion of a normal vessel (Fig. 11) is most commonly seen after splenectomy or in cases of polycythaemia vera. It is characterized by the rapid accumulation of ascites, melaena, colicky abdominal pain, and ileus. If the spleen is still present and has not already been enlarged by the predisposing disease, it may rapidly increase in size. Death follows within a few days.

The second syndrome appears usually in patients with previous hepatic disease. This may be an early fibrosis or a chronic infiltration such as can occur in lymphadenoma. Splenomegaly and ascites suddenly develop. Haematemesis is common, but the other intestinal symptoms of the acute syndrome are lacking. Death usually occurs [illegible]

of ascites, but at autopsy show no thrombosis of the portal vein. The subsequent rapid development of collateral veins renders the diagnosis more probable.

Occlusion of the Hepatic Artery

Occlusion of a previously healthy hepatic artery is a rare event occurring most commonly in periarteritis nodosa or from embolism in subacute bacterial endocarditis [11, 15, 17]. When the main artery is suddenly and completely occluded, as by a ligature, and there are no collateral channels, death in coma follows in one or two days.[11] When a main branch of the artery is involved, as in periarteritis nodosa, jaundice and fever and pain over the right lower ribs, exacerbated by respiration, develop.[20]

Occlusion of the Hepatic Veins

Such occlusion may occur from thrombosis or an obliterating endophlebitis.[5]

Thrombosis of the hepatic veins leads rapidly to ascites, splenomegaly and enlargement and tenderness of the liver, often with jaundice. It may be combined with partial or complete occlusion of the inferior vena cava in which case swelling of the legs and, subsequently, collateral vessels carrying blood upwards from the femoral veins develop.

Obliterating endophlebitis may be either acute or chronic [14, 21]

CHAPTER XI

CIRCULATORY DISORDERS; FOCAL LESIONS; AND CANCER OF THE LIVER

THERE remain to consider three groups of conditions: circulatory disorders, focal lesions, and cancers of the liver. The pathology of the *first two groups has already been discussed; the relationship of primary* cancer to post-necrotic scarring has been indicated. For the sake of completeness their significant clinical features will now be described.

CIRCULATORY DISORDERS OF THE LIVER

Inadequacy of the circulation in an organ may be either absolute or relative. In the former the requirements of the hepatic parenchyma are normal but the circulation through it is reduced; in the latter the circulation is unimpaired but the requirements are greater than it can meet Absolute inadequacy is seen in vascular occlusion, cardiac failure and, perhaps, in post-traumatic states associated with prolonged arterial hypotension; relative inadequacy in thyrotoxicosis.

VASCULAR OCCLUSION

More often than not occlusion of either of the vessels carrying blood to the liver is an unexpected finding at autopsy. This is because the great majority of occlusions occur in vessels in which chronic disease of the wall, or of the hepatic tissues through which it passes, has already produced partial obstruction and, in consequence, the formation of a collateral circulation adequate to accommodate the blood-flow when occlusion occurs. Such occlusions, being compensated, produce few, if any, symptoms during life. To see the syndromes peculiar to occlusion of the portal vein, the hepatic artery or the hepatic vein attention must, therefore, be directed to patients with little or no previous disease of those vessels or their surrounding structures

Thrombosis of the Portal Vein

Two syndromes can be correlated with thrombosis of the portal vein; one with acute and complete occlusion of a normal vessel, the other with partial occlusion of a normal vessel or complete occlusion

-dvanced, liberation lead to disappear- normal. In more advanced cases, however, the fibrosis may have reached the 'irreversible stage' described by Cameron and Karunaratne,[46] be too well-established to regress and, just as in any other type of hepatic fibrosis, the liver lesion will then progress until, ultimately, it may produce the symptoms of diffuse hepatic fibrosis

The development of hepatic fibrosis in the presence of chronic congestion of the liver presents no difficulty. Such congestion leads to centrilobular necrosis and, as has been mentioned, long continued or repeated attacks of centrilobular necrosis, however produced, lead eventually to the gradual development of a diffuse hepatic fibrosis.

HEPATIC LESIONS IN THYROTOXICOSIS

Both acute and chronic hepatic lesions are known to occur in patients with thyrotoxicosis [1 4 16 23] The acute lesions are fatty infiltration, centrilobular, and sometimes even massive, hepatic necrosis These are found in patients who have died as a direct result of severe thyrotoxicosis The chronic lesions may have the features either of diffuse hepatic fibrosis or of post-necrotic scarring, sometimes both are

lesions Given that thyroxine can lead, or predispose, to centrilobular necrosis, their explanation is not difficult Repeated exacerbation of thyrotoxicosis by producing repeated attacks of such necrosis would lead to a diffuse hepatic fibrosis An episode of thyrotoxicosis so serious as to become a thyroid crisis might well lead to centrilobular necrosis of such severity as to become massive in extent. If the patient survives, post-necrotic scarring and nodular hyperplasia develop at the sites so affected

may be of practical benefit

The former is indistinguishable from thrombosis of the hepatic veins. The symptomatology of the latter is qualitatively similar but more chronic in its course and may lead to the development of hepatic fibrosis. Syphilis is one of the few known predisposing causes of this condition.

CARDIAC FAILURE AND LIVER DISEASE

An enlarged liver is a frequent accompaniment of congestive cardiac failure The enlargement is uniform, and, if it occurs rapidly, tenderness, distension pain and, often, vomiting are present. In severe cases ascites develops, but splenomegaly is usually absent unless some complication such as subacute bacterial endocarditis is also present.[7] The ascites, in acute cases, is related to the degree of venous congestion. It is presumably due to the damming back of blood in the territory drained by the portal vein giving rise to portal hypertension and, perhaps, to anoxia with a consequent increase in permeability of the capillary walls in that territory.

In the course of heart disease, jaundice or hepatic fibrosis may appear.[2, 6, 23] Their appearance is correlated with cardiac failure. Two suggestions have been made to explain the occurrence of jaundice; one that it is the result of impairment of the liver function, the other that it is due to an excess of bilirubin liberated from pulmonary infarcts[6] If the latter explanation were correct one would expect jaundice to be a feature of pulmonary infarction even in the absence of gross cardiac failure Experience shows that it is not As a rule jaundice only occurs in the presence of severe right-sided failure of the heart, and in such cases the liver is usually enlarged and tender and shows centrilobular degeneration at autopsy (Figs. 13, 14). The general trend of evidence would seem to point to *functional impairment of the liver as the cause*.

A diffuse hepatic fibrosis occurs in association with heart disease under two *conditions; in cases of chronic congestive cardiac failure,* [illegible]

hepatic lesion to become clinically important, although at autopsy it is common to find the condition well established. Constrictive pericarditis is, however, compatible with years of life, and in such cases the chronic congestion of the liver, due to mechanical constriction of the inferior vena cava, has time to produce a diffuse hepatic fibrosis of

they become infected they rarely produce symptoms other than an actual lump. The commonest site for their development is in the right lobe, and they not infrequently project downwards and inwards below the costal margin. In that site they may be recognized at a glance for, having been present for years, the costal margin has become moulded to the protuberance on the anterior surface of the liver.

Suppurative Pyelophlebitis

In this condition pyaemic abscesses are disseminated throughout the liver in association with the terminal branches of the portal vein. It occurs secondary to sepsis in the territory drained by the portal vein. The condition is ushered in by rigors, and high fever follows. The

Jaundice is unusual and if found, particularly if its onset preceded the fever, the diagnosis should be doubted and the presence of a suppurative cholangio-hepatitis suspected. Most patients with this condition die, often within a few days, but sometimes they linger for two or three months. Two components enter into these cases: the septicaemia and parenchymal failure consequent upon the inflammation of the parenchyma contiguous to the abscesses. The relative importance of these varies from case to case but, on the whole, while septicaemia predominates in the short-lived, parenchymal failure becomes of increasing importance with each week of survival.[13 20]

CANCER OF THE LIVER

Primary Carcinoma of the Liver

Primary carcinoma of the liver usually, if not always, develops in a liver which is already the seat of fibrosis The more pronounced the hyperplasia in the fibrotic liver the more likely is primary cancer to arise. Such carcinomata are, therefore, particularly apt to occur in chronic massive hepatitis, in which condition nodular hyperplasia is conspicuous (Figs. 42, 43). It would be misleading, however, to imply that primary hepatic cancer only occurs in this condition It may occasionally supervene on diffuse hepatic fibrosis

The diagnosis can rarely be more than suspected during life Usually all that is noted is that a patient with hepatic fibrosis begins to fail rapidly. At autopsy the supervening primary carcinoma is disclosed. Sometimes, however, it may be noted that one part of the fibrotic liver is rapidly enlarging. Often the peritoneal type of hepatic pain is

FOCAL LESIONS OF THE LIVER

Focal lesions of the liver do not produce symptoms referable to that organ unless they are so numerous, or so large, as to damage the major part of it. In the course of many forms of illness, in which septicaemia is present at some period, microscopic foci of acute necrosis are discovered at autopsy scattered throughout the liver. As a rule they occupy only a portion of the lobule, usually in the mid-zonal region. Clinically, they have neither immediate nor remote significance.

Larger inflammatory masses occur in the form of gummata. In the early stage these may stand out from the surface of the organ and be palpable through the abdominal wall. There are rarely more than two or three such masses, but the local lesion does not represent the whole extent of the damage. For a considerable distance round each gummatous mass the liver is involved in an inflammatory reaction, and the total amount of liver so involved may be such as to lead to functional impairment Enlargement of the liver usually, and jaundice sometimes, occurs. It is uncertain whether the jaundice is due to a widespread inflammation or to the inflammatory masses causing an intrahepatic biliary obstruction. In many cases ascites develops, only to disappear spontaneously as the gummata heal. While present it may be sufficiently severe to require repeated paracentesis. Its explanation is uncertain. In a few cases it is associated with syphilitic nephrosis, in a larger number, thrombosis of the inferior vena cava is subsequently recognized Gummata heal by fibrosis. The inflammatory processes in the intervening areas subside and ultimately the patient is left with a characteristically shaped liver. The borders are rounded, and two or three deep scars, cutting into the liver substance, produce a corresponding number of deep indentations in its lower edge. Between the scars the liver tissue is normal. This hepar lobatum is often sufficiently marked to be [illegible] Splenomegaly is usually ass[illegible] that such is secondary to [illegible] suffered by many of the [illegible] rosis, *having* ample amounts of normal parenchyma, live for years without hepatic failure. Sometimes the fibrosis is more widespread and in such cases the syndrome of portal obstruction may develop. More frequently, however, the patient's health is unaffected and he dies, many years later, of some other condition.

Echinococcal cysts of the liver may be conveniently considered along with such large space occupying masses as gummata. Unless

The local symptoms of secondary cancer are enlargement of the liver and pain. Clinically, the enlargement may appear to be nodular or diffuse, although at autopsy the difference is seen to be one of degree in the size and dissemination of the nodules. The liver with secondary cancerous deposits projecting as hard, craggy, masses from its surface and lower border is familiar. That secondary cancer may produce a general enlargement of the organ in which the normal anatomical shape is retained is not so well-known. Such general enlargements may resemble hepatic fibrosis, and it is only when typical craggy growths develop that their nature is revealed

Pain in secondary cancer of the liver may be of two types: that associated with rapid enlargement of the organ and that from irritation of the peritoneum That associated with enlargement ranges from a dull sense of weight or fulness in the abdomen to acute upper abdominal pain of such severity as to suggest an acute surgical emergency. The peritoneal type of pain is usually of sudden onset and may be the symptom which prompts the patient to seek advice. It is often made worse by movement and breathing, but may disappear spontaneously for two or three days at a time Sometimes such pain is referred to the

These various symptoms associated with secondary cancerous

the liver is uniformly enlarged One is the syndrome of rapid enlargement, the other of slow. The syndrome of rapid enlargement due to secondary carcinoma in the liver may closely resemble that of a subphrenic abscess

A man, aged 54 years, played and won a golf tournament and thereafter celebrated

after the onset of pain he was complaining of severe pain in these sites, which was persistent, but made worse by breathing The man was obviously suffering greatly.

experienced in association with this. The enlargement is hard and, it being known that fibrotic livers do not enlarge of themselves, the suspicion arises that a new growth is present. Secondary malignant deposits in the lungs being common, haemoptysis is a frequent symptom

Secondary Cancer of the Liver

Secondary neoplasms in the liver may arise from primary growths situated in any organ of the body. They may be either carcinomata or sarcomata. The primary growth may materially contribute to the symptomatology of the particular case; or it may be completely unobtrusive. The symptomatology actually referable to the secondary *deposits in the liver falls under two headings: the general and the local* effects.

It is commonly held that, among the general features of secondary hepatic cancer, wasting is early and prominent. This view derives from the fact that such cancers are often secondary to primary growths in the alimentary tract which, if appropriately situated, can themselves cause wasting. But if attention is directed to those cases with hepatic cancers, secondary to growths in other regions of the body, it will be seen that loss of weight is seldom conspicuous until the later stages. Thus the liver may reach an enormous size from cancerous deposits, if the primary growth is a carcinoma of the bronchus or a melanoma of the uveal tract, and yet the patient appear plump and well-nourished. It is surprising how extensive the cancerous deposits may be without producing signs of liver failure. The only type of functional failure which is commonly seen is failure to excrete bile. Jaundice, of the obstructive type, occurs in a considerable proportion of cases. It is presumably due to pressure by the deposits of growth on the biliary passages. Apart from this the other functions of the liver are usually surprisingly well-preserved until the last few days of life.

Among the general symptoms, for which there is as yet no adequate explanation, fever requires notice It is not common, occurring in only about one-seventh of the cases. The different types range from a [illegible] tained temperature. When [illegible] ytosis which reaches levels [illegible] In such cases the erythrocyte sedimentation rate is also high. In general this febrile reaction is seen in association with rapidly growing cancers which are often undergoing necrosis in their central parts. *It has been ascribed to the* products of such necrosis being pyrogenic.

The syndrome of slow cancerous enlargement of the liver is seen in

loss in weight

palpable Three months later he died. The liver had increased in size and towards the end had become nodular At autopsy it was almost entirely occupied by secondary carcinoma It weighed 7 kilogrammes The primary growth was a small carcinoma in the left bronchus which had given neither signs nor symptoms referable to the lungs during life

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The temperature was 103° F, the pulse rate 124 a minute. The tongue was furred. On examination the liver edge was felt two fingers' breadth below the right costal

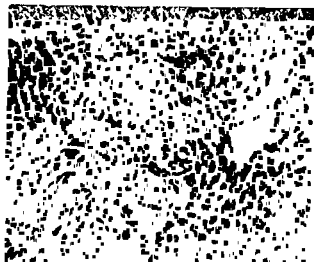


FIG 61—Secondary cancer in the liver The cancer in this case has spread rapidly, from the primary growth in the stomach, through the portal vein Nests of cancer cells can be seen in that vessel and in the sinusoids H and E × 122

margin It was tender The edge was sharp, firm rather than hard, and inclined smoothly upward to the left across the abdomen The spleen was not enlarged.

was much urobulin in the urine, but not bilirubin, and no clinical evidence of jaundice At operation a cancerous ulcer was found on the lesser curvature of the stomach. The liver was enlarged and bulged into the wound It was purplish in colour, but through the injected peritoneum pale areas varying from a one or two millimetres to a centimetre in diameter were seen A biopsy of the liver was taken and on examination showed that the growth was being disseminated through the portal vein (Fig 61) In the veins of the portal tract and in the sinusoids masses of carcinoma cells were to be seen. The explanation of the symptomatology was now clear. Cancer cells had been widely and rapidly disseminated through the liver where they had lodged and grown rapidly As a result the organ had enlarged, but uniformly, because of the even distribution of the process This enlargement had been so rapid as to produce severe abdominal pain, tenderness and vomiting, just as occurs with the rapidly enlarging liver in cardiac failure and the pre-coma stage of diabetes Finally the growth had reached the peritoneum on which, as shown by the dilated capillary vessels, a reaction had occurred And as a result of this peritonitis the man had sharp pain on breathing

functional disturbances present at a particular time. In this it differs from long-term treatment, which, like prevention, is more closely related to considerations of aetiology.

It thus seems that we have reached a position in regard to our knowledge of diseases of the liver when, having progressed beyond the stage of simply collecting observations, we can begin the grouping of related phenomena into categories. As always, this will reveal large gaps in our factual knowledge and will necessitate frequent returns for the collecting of further, and the more precise definition of old, observations But there will be a difference. At the purely observational stage the collecting of facts is undirected and largely determined by chance, in the stage of categorization it is directed to a definite purpose—to answer precise questions Progress in the accumulation of knowledge may, therefore, be expected to accelerate The observer can now become the investigator But investigation brings its own dangers. The progress of knowledge can be as effectively impeded by a misconceived hypothesis as by factual ignorance It is, therefore, incumbent upon all investigators to submit any suggested correlation of data, whether advanced by themselves or by others, to repeated and stringent criticism The groupings and sequences put forward in these lectures are offered in this understanding. Founded as they are on our present incomplete knowledge it would be surprising if any were wholly correct, but it is hoped that most may serve to focus

cellular activity where the distinctions between structure and function disappear in a common basis of chemistry and physics

CHAPTER XII

CONCLUSIONS

THE tentative classification of disease of the liver, previously suggested, has now been illustrated by a brief survey of the clinical forms of such diseases. It is evident that these forms fall into various, more or less, definite sequences, and that these correspond to the pathological sequences observed both in man and experimental animals. The recognition of such sequences is of twofold importance. By clarifying the natural history of different lesions it places prognosis on a firmer basis. By relating one pathological form to another it enables the initial lesion of each sequence to be recognized. This latter is of particular importance when, as in the case of the liver, the organ affected possesses such reserves of function that it is not until damage [illegible]

recoverable, susceptible to therapy and even to prevention. It is by directing therapeutic and preventive measures against such early stages that the most effective results can be expected.

But, however useful the recognition of the different sequences may [illegible] to the [illegible] liver [illegible] fully supports the conclusion derived from a study of its pathology, namely, that the same type of liver injury may, on occasion, be caused by several different factors As a consequence the clinical manifestations of liver injury from widely different causes may be indistinguishable, and it is only by attention to the concomitant general effects of the causative agents, or to such circumstantial evidence as exposure to special conditions, that the exciting cause of the illness can be recognized. Only in the broadest sense can the clinical manifestations of liver injury be related to the particular pathological lesion present Symptomatology is the expression of deranged function and, although gross alterations in structure lead to such derangements, disturbances of function may occur from lesions too subtle to cause structural alterations Nevertheless, by analysing the symptomatology of established pathological lesions, it is possible to see its broad correlation with

development of histo-chemical techniques will provide a sound basis

functional disturbances present at a particular time In this it differs from long-term treatment, which, like prevention, is more closely related to considerations of aetiology.

It thus seems that we have reached a position in regard to our knowledge of diseases of the liver when, having progressed beyond the stage of simply collecting observations, we can begin the grouping of related phenomena into categories As always, this will reveal large gaps in our factual knowledge and will necessitate frequent returns for the collecting of further, and the more precise definition of old, observations But there will be a difference. At the purely observational stage the collecting of facts is undirected and largely determined by chance, in the stage of categorization it is directed to a definite purpose—to answer precise questions. Progress in the accumulation of knowledge may, therefore, be expected to accelerate The observer can now become the investigator. But investigation brings its own dangers. The progress of knowledge can be as effectively impeded by a misconceived hypothesis as by factual ignorance It is, therefore, incumbent upon all investigators to submit any suggested correlation of data, whether advanced by themselves or by others, to repeated and stringent criticism. The groupings and sequences put forward in these lectures are offered in this understanding. Founded as they are on our present incomplete knowledge it would be surprising if any were wholly correct, but it is hoped that most may serve to focus

some functional—into a more comprehensive classification But such broad generalizations lie still in the future. When they emerge it is probable that they will be found to derive from that level of intracellular activity where the distinctions between structure and function disappear in a common basis of chemistry and physics

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